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FURTHER STUDIES ON THE THYMUS AND PINEAL GLANDS*

By L. G. ROWNTREE, M.D., F.A.C.P., J. H. CLARK, M.D., F.A.C.P., A. STEINBERG, B.S., A. M. HANSON, M.D., N. H. EINHORN, M.D., and W. A. SHANNON, M.D.,

Philadelphia, Pennsylvania

THE results of our early studies on the biological effects of thymus extract were published in July 1934. In the present communication we wish to present further studies on the thymus gland, up to April 8, 1935, and also the biological effects of pineal extract (Hanson) when administered to succeeding generations with the identical procedure followed in our thymus studies.

FURTHER STUDIES OF THE THYMUS GLAND

Our knowledge of the physiology of the thymus dates from Friedleben in 1858 who found that it was indispensable to life and was concerned in some way with blood format. with nutrition and with growth. In 1908 Basch demonstrated that it concerned with calcification of bone and intimated its importance in tl young. Hewer (1915) and Nitschke (1928) have concurred in this idea. An important series of studies were carried on by Klose and Vogt between 1910 and 1914 indicating that thymectomy in young dogs resulted in adiposity, subsequently in cachexia and finally in death. An excellent critical review, together with the results of their own careful experiments, was published in 1919 by Park and McClure. Their results were entirely negative.

On the biological side, Gudernatsch (1913) found that tadpoles grew

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From the Philadelphia Institute for Medical Research, from the Samuel Bell, Jr., Laboratory in the Philadelphia General Hospital, the Laboratories of the Philadelphia General Hospital, Philadelphia, Pennsylvania, and the Hanson Research Laboratory, Faribault, Minnesota.

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very large without metamorphosis when they were fed thymus glands. Uhlenhuth confirmed these findings but explained them on a nutritional basis. Gudernatsch also showed that feeding of thymus glands in rats through several successive generations resulted in large, well nourished offspring. Another interesting phase of the study of thymus has to do with eggshells. Soli found that thymectomy caused pullets to lay eggs lacking in shells. Oscar Riddle, finding pigeons laying eggs without shells, treated them with thymus gland which resulted in the laying of normal eggs. Perhaps the most significant work in relation to the biological effect of the thymus gland has been carried on in Asher's laboratory where Victor Nowinski utilized an aqueous extract of thymus called thymocrescin. He found that under its influence rats that were losing weight on a low vitamin diet returned to normal weight. He concluded that the thymus gland has something to do with growth and also with the size of the gonads.

Our experiments were conducted as follows: 1 c.c. of thymus extract (Hanson) has been administered to rats intraperitoneally daily even through the periods of pregnancy and lactation. As their offspring reach a suitable age, either prepubertally or maturely, they are mated and likewise injected. This has been carried on through succeeding generations and the effect on both parents and offspring noted. The results up to and including the fifth generation have already been presented.[1] The work has been continued now into the tenth generation. In addition we wish to present the results of thymectomy in succeeding generations of parents upon the growth and development of their offspring.

The Rate of Growth and Development in the Sixth (F_6) Generation. The sixth generation consisted of 82 rats born to four pairs of fifth generation rats. The average birth weight was 5.5 gm. (control, 4.6 gm.). The ears were open almost invariably on the first or second day (control, 2½ to 3½). Teeth were erupted at one day (control, 8 to 10). Hair appeared at two days (control, 12 to 16). The eyes opened between the second and third day (control, 14 to 17). The testes descended by the fourth day (control, 35 to 40). The vagina opened on the seventeenth day (control, 55 to 62). Seventy-five per cent of the young survived (control, 37.8 per cent). The rate of growth and development in this generation was more rapid than any encountered earlier.

The Rate of Growth and Development of the Seventh (F_7) Generation. The seventh generation consisted of 93 rats born to five pairs. The average birth weight was 5.6 gm. Eighty-four per cent of the young survived. The ears were open in some instances on first inspection; only occasionally was this delayed until the first day. The teeth likewise were erupted sometimes at birth, usually in the first 24 hours. Hair appeared as a rule on the first or second day. The eyes opened at one and one-half to two days. The testes descended from the fourth to the fifth day. The vagina opened in every instance by the twenty-fourth day, most frequently from the sixteenth to the eighteenth day. One pair of the seventh generation became

pregnant as early as the forty-sixth day and delivered on the sixty-eighth day. (Figure 1.)

The Rate of Growth and Development in the Eighth (F_7) Generation. The eighth generation consisted of 48 rats born to four pairs. The average

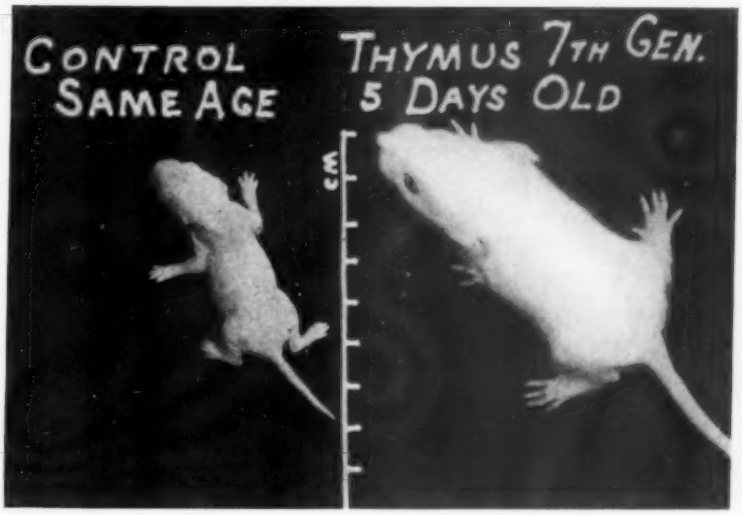

FIG. 1.

birth weight was 5.4 gm. Ninety-three per cent survived. In this group the ears were open on the first inspection, at six hours or at least within 24 hours. The incisors were erupted as early as eight hours and in every instance on the first day. Hair appeared on the first or second day. The eyes opened as early as 42 hours. The testes descended on the third to the fourth day and the vagina opened on the sixteenth day. One pair became pregnant as early as the thirty-fifth day. Two litters were born under 60 days.

The Rate of Growth and Development in the Ninth (F_8) Generation. The ninth generation consisted of 33 rats born to three pairs. The average birth weight was 6.3 gm. One hundred per cent of the young survived. The ears were open at birth or on first inspection within 24 hours. The incisors were erupted at birth or within 24 hours. Hair appeared on the first day in moderate amounts, the animals being covered with a profuse fur within two days. The eyes began to open as early as 42 hours, and this was completed, in every instance but one, in 43 hours. The testes descended on the third to the fourth day and the vagina opened on the sixteenth to the seventeenth day. One of these pairs became pregnant on the twenty-second day and cast a litter on the forty-third day. The mother, four days prior to delivery, weighed 102 gm. and after delivery five rats weighed 90 gm.

The Rate of Growth and Development of the Tenth (F_9) Generation.

The tenth generation consisted of one litter of eight with a birth weight of 6 gm. Seven young survived. The ears were open and the teeth were present at first inspection. Hair appeared in six hours. The eyes were opened in 36 to 40 hours. The testes were descended by the third day and the vagina was opened on the sixth day, estrus following within three days as shown by smears.* The rats of the tenth generation were from the standpoint of every criterion the most precocious observed in the study to date.†

Activity and Behaviorism of Rats under the Influence of Thymus Extract (*Hanson*). The psychic precocity is as striking as the physical in the thymus treated strain of rats. Thus, rats of the fifth to the tenth generation test strain run about the cage at from two to three days of age and are as alert as normal rats of 16 to 20 days of age. These animals will climb out of a wire net enclosure from 3 to 4 inches high and manifest all the activities of normal animals four or five times their age. Weaning is possible as early as 48 hours, the little rats finding their own supply of water, milk and food. They nest, burrowing under the excelsior, and find a resting place and have no need of further care from the parents. The weaned animals have fared as well, and in some instances better, than their litter mates left with the parents. The thymus treated animals appear to be healthy, contented and docile. Their actions, asleep or awake, resemble those of normal controls in every way.

Rats of the advanced generations can swim as early as the third day. The growth in these generations as in the earlier ones is affected only in the early days of life, more especially before the sixteenth day. Giants do not develop.

It is interesting to note, we believe, that the original pair of thymus test animals are still living after 25 months and that they have lived to see their descendants into the tenth generation.

In the animals of the third to the tenth generations striking and accruing precocity, and acceleration in growth and development, were noted in the offspring of each succeeding generation under treatment. The normal rate of growth and development and the precocity resulting from continuous administration of thymus extract through succeeding generations are shown in the accompanying table. (Table 1.)

The increasing growth as indicated in weight curves is shown in the accompanying figure. (Figure 2.)

The Effects of Thymectomy in Successive Generations. A study of the effects of thymectomy in successive generations of parents upon the rate of growth and development in the young is being undertaken by Dr. N. H. Einhorn and Dr. W. A. Shannon. The removal of the thymus appears to

* This phenomenon awaits histologic confirmation of findings in the ovary.

† With the original extract the effects on acceleration of growth and development were extremely consistent. Since that supply was exhausted and we have been utilizing batches of thymus extract made up in the Institute there has been more variability especially in relation to weight.

TABLE I

Development of Thymus Treated Rats and Their Controls

	Controls	F_1.	F_2.	F_3.	F_4.	F_5.	F_6.	F_7.	F_8.	F_9.
Aver. Birth Wgt. (gm.)	4.6	5.1	5.3	5.3	5.6	5.5	5.6	5.5	6.5	6.0
Ears Opened (days) . .	2½–3½	2–3	2	1–2	1–2	1–2	½–2	Birth	Birth	Birth
Incisors Erptd. (days)	8–10	8–9	4–6	4–6	2–3	2	1–2	Birth	Birth	Birth
Hair Appd. (days)	12–16	10–12	4–6	4–6	2–3	2	1–2	1–2	1	1
Eyes Opened (days) . .	14–17	12–14	4–6	4–6	2–3	2–3	2–3	42–48 hours	42–48 hours	36–42 hours
Testes Dscd. (days) . .	35–40	15–29	15–21	10–12	6–10	4–6	3–10	3–4	3–4	2–3
Vagina Opened (days)	55–62	30–45	23–32	21–27	18–20	18–20	16–20	16–18	16–18	6
Pregnant (days from birth)	80	70	56	42	25	40	46	37	22	—
First Litter Cast (days from birth)	102	92	78	64	47	61	68	59	43	—

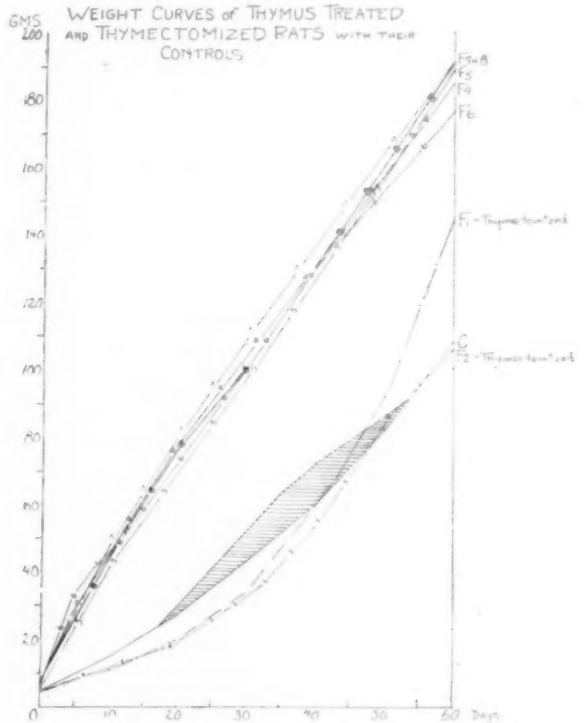

FIG. 2.

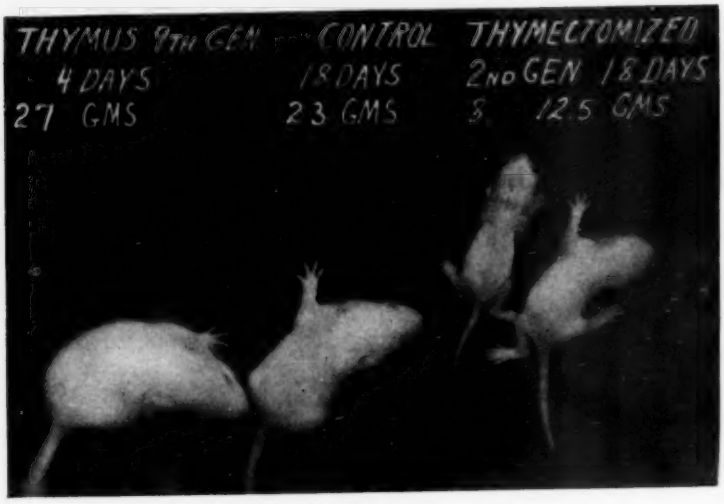
THYMUS 9TH GEN
4 DAYS
27 GMS
CONTROL
18 DAYS
23 GMS
THYMECTOMIZED
2ND GEN 18 DAYS
♂ 12.5 GMS

FIG. 3.

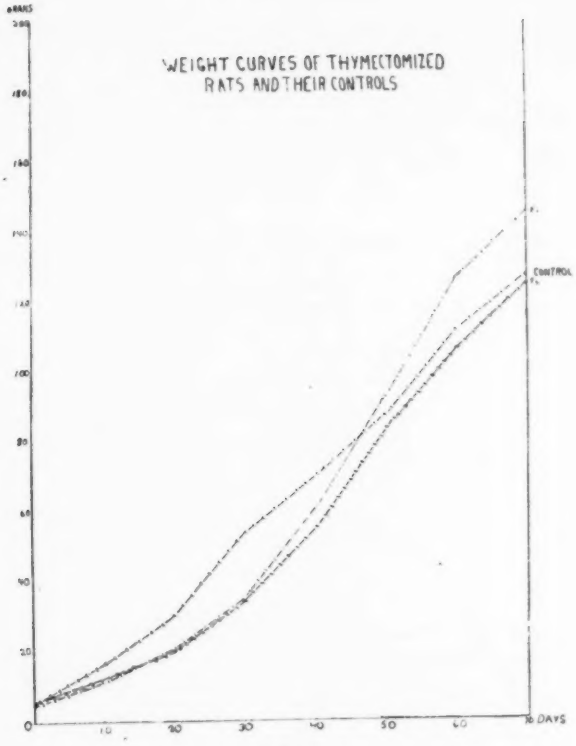
WEIGHT CURVES OF THYMECTOMIZED
RATS AND THEIR CONTROLS
CONTROL
DAYS

FIG. 4.

retard growth in the second and third generations but the effect on differentiation is not so striking. In practically all of the young born, the eruption of teeth, the opening of the eyes, the growth of fur, etc., is within normal time but usually at the lower extreme of normal. Thus the eyes open on the sixteenth day, occasionally on the seventeenth or eighteenth day, but at least up to the third generation there is no abnormal retardation in development. (Figure 3.) The effects on growth, as revealed in the weight curves, can be seen from the accompanying figure. (Figure 4.)

It would appear, therefore, that thymectomized rats are retarded in growth during the first 10 weeks of life, the weight curves lagging below the normal to the extent of 25 to 30 per cent. After maturity the weight curves are essentially normal.

Further Studies of the Pineal Gland

The success attending our studies with the continuous administration of thymus extract (Hanson) to successive generations of parent rats, resulting in the remarkable precocity in the offspring of the third and succeeding generations, led us to attempt the same procedure with an extract of the pineal gland.

Experimental Procedure. A small colony of four pairs of albino rats (Wistar strain) was started on pineal extract on March 2, 1934. Test animals have been subjected to date to 1 c.c. intraperitoneally of pineal extract daily even during periods of pregnancy and lactation. Offspring born to these rats have been mated in pairs and these likewise have been so treated and the effects of pineal extract on parents and offspring noted.

Thus the original test animals of the first generation (F_0) have undergone continuous treatment since March 2, 1934; the second generation (F_1) since April 2, 1934; the third generation (F_2) since September 18, 1934; the fourth generation (F_3) since November 12, 1934; and the fifth generation (F_4) were started on this treatment on March 18, 1935.* In the offspring, treatment was begun, in the prepubertal group, from the sixteenth to the twenty-fifth day and, in the mature group, from the fortieth to the sixtieth day. At the present time we have reached the fifth generation of pineal treated rats and have over 300 such in this colony.

The Nature of the Pineal Extract Used. The pineal extracts which we have employed were made from pineal glands from beef of average killing age. Several such extracts have been prepared, namely P. B. No. 22 to No. 29 inclusive. The most potent of these was found on investigation to be P. B. No. 22. No effects were observed as a result of administering extracts P. B. No. 23 to No. 27 inclusive. P. B. No. 28 and No. 29 are being subjected to assay at the present time. To date, however, none appear to be preferable to the original extract employed, P. B. No. 22. This is a slightly turbid, somewhat greenish looking solution, nonirritating locally and relatively non-toxic to rats in doses of 1 c.c. intraperitoneally.

*In the text, F_0 animals are referred to as first generation and F_4 as fifth generation respectively.

In preparing this extract, beef pineal glands were secured at the kill and frozen in dry ice, with as little delay as possible. The glands were ground in their frozen state and each 100 gm. transferred to a four-liter beaker of Pyrex glass. Two thousand c.c. of a 0.1 per cent HCl by volume are then added, the beaker placed over a Bunsen flame on a tripod with asbestos screen, utilizing a mechanical stirrer with a heavy glass stirring rod which is introduced to within ½ inch of the bottom of the beaker. The heating is continued until the temperature reaches 89 to 90° C., when the flame is turned off and 200 c.c. of an ethyl-methyl alcohol mixture added and the stirring continued for one hour.*

At the end of one hour, the mechanical stirrer is stopped and the extract filtered through cotton covered with gauze to separate the solution from the solid matter. The extract is then made up to 2,000 c.c. with boiled distilled water and 1.25 volume of filtered saturated aqueous picric acid added. It is allowed to stand until the picrate precipitate has settled to the bottom of the beaker when most of the supernatant fluid is poured off and the remainder with the precipitate poured on filter paper and allowed to drain over night. The picrate, drained almost dry, but still moist, is removed from the filter paper and transferred to a Pyrex glass beaker of suitable size and extracted in 1000 c.c. of a 0.25 per cent HCl by volume with constant stirring and heat to 89 to 90° C., made up to its original volume with boiled distilled water and 1 c.c. of a 91 per cent aqueous solution of phenol added and the extract transferred to a sterile one-liter Pyrex glass flask, capped and cooled to minus 12° C., allowed to stand four hours, or over night, filtered, made up to 1100 c.c. with boiled distilled water, heated to 89 to 90° C., 4 c.c. of a 91 per cent aqueous solution of phenol added as a preservative and the extract transferred to sterile 50 c.c. rubber capped bottles.

Controls Employed. The controls were of several kinds: (*a*) the strain of rats which constituted the controls for our earlier thymus studies; (*b*) the published data obtained in the study of rats at the Wistar Institute, summarized in *The Rat* by Dr. H. H. Donaldson (Cf. table 2); (*c*) animals injected with 0.21 per cent picric acid solution over a period of several weeks, none of which evidenced any demonstrable biologic effects. In our opinion picric acid is definitely eliminated as a factor in the effect observed.

The Effects of Pineal Extract in the First (F_0) Generation. Pineal extract has been administered to this group, four pairs of rats, over a period of more than 12 months. While acute toxic effects have not been observed from the small doses employed, the general effect has been one of a mild deterrent to health and growth. All of the surviving animals concerned are now from 450 to 480 days of age. They are decidedly underweight for their present age. In this connection it should be remembered that treatment was begun in these rats when they were mature, at an age of 84 days. In addition the males present some suggestion of an abnormal condition of

* The ethyl-methyl alcohol mixture must be freshly prepared each time and is made up as follows: ethyl alcohol, 95 per cent, 20 c.c.; and methyl alcohol, synthetic, C. P., 180 c.c.

TABLE II

Comparison of Control Rats with Those of the Wistar Institute *

	Strain	
	Wistar Institute	Philadelphia Institute for Medical Research †
No. in litter	6.1	4.9
Ears open	2½ to 3½	2½ to 3
Teeth erupted	8 to 10	9 to 10
Hair appeared	16	12 to 16
Eyes opened	14 to 17	14 to 17
Testes descended	40	31 to 40
Vagina opened	72	55 to 62
Comment	On a varied breeder's diet	On an adequate stock diet

* The measure of time is days.
† Based on 104 animals.

the external genitalia, enlargement of the penis, possibly priapism or sex excitation and frequently paraphymosis. From the behavioristic point of view these rats appear to be tense and more irritable than normal.

Growth and Development of the Second (F_1) Generation. In all, 138 rats were born in the second generation to four pairs of test animals of the first generation under treatment. The biologic data indicate normal and in some cases rapid breeding on the part of the parents, an average period between the casting of litters of 39.6 days for the test animals as compared with 42.5 days for the controls. The average litter consists of 5.1 rats which closely approximates that of our normal controls (4.9). The animals at birth averaged 4.9 gm. which is slightly higher than the normal (4.6). Fifty per cent of the offspring of the test animals survived as compared with 37.8 per cent of the offspring of the controls.

No definite departure from normal was noted in this generation in the earlier litters relative to the opening of the ears, the eruption of teeth, the development of fur, or the opening of the eyes. However, growth was retarded while gonadal development and maturity were somewhat earlier than normal. Also, the penis was enlarged. The testes in all males descended in less than normal time, from 36 to 12 days, at an approximate average of 22 days for the entire group, as compared with the normal (31 to 40). The tendency to early descent is more apparent in the later litters born to the same parents. Thus, in the offspring of No. 500 to No. 501, the testes descended in 31 days in the first litter cast after treatment was begun and in 12 days in the ninth litter (one animal); in the offspring of No. 502 to No. 503 in 26 days in the first and 20 days in the sixth litter; in the offspring of No. 508 to No. 509 in 30 days in the first and in 16 days in the fifth litter. Likewise earlier maturity was encountered in the female, the vagina opening between the fifty-second and the thirty-second day, at an approximate average of 45 days, as compared with the normal of 72 to 55 days.

Variability in the survival rate is worthy of comment. It is rather striking that in the first three litters born to pair No. 500 to No. 501, 100 per

cent survived; whereas in the remaining eight litters, there were but five survivals out of 51 animals. Of the offspring of No. 506 to No. 507, only five animals survived out of 15 born, all being of the fourth litter. The highest survival was among the offspring of No. 508 to No. 509, 15 out of 22 animals.

It is interesting also to contrast the first with the tenth litter born to No. 500 to No. 501. In the first litter cast after treatment was begun all survived and the animals conformed to normal standards throughout except that growth was retarded and the testes descended on the thirty-first instead of the fortieth day, whereas in the ninth litter only 1 of 13 survived and in this rat the teeth erupted at 7 days, hair appeared from the ninth to the eleventh day, the eyes opened at 12 days, the testes descended at 12 days. Mild precocity in hair growth and gonadal development is shown also in the last litter born to pair No. 502 to No. 503. Hair appeared at 12 to 14 days; the eyes opened at 12 days; testes descended at 20 days (two males only surviving).

Although the birth weight of these rats was normal, growth, as indicated by the weight curves, was decidedly retarded. At 10 days the pineal test strain were at least 25 per cent under normal and at 30 days more than 30 per cent below standard.

The Growth and Development of the Third (F_2) Generation. In test animals of the third generation, i.e. animals born to two generations of rats treated with pineal extract, the effect on growth and development was considerable. In all, 543 animals were born in 93 litters to 18 pairs of second (F_1) generation rats under treatment with pineal extract (Hanson). The interval between gestations was 33.8 days as compared with 42.5 days for the controls. An average of 5.6 rats per litter was cast as compared with 4.9 for the controls. The average birth weight was 4.6 gm. for the test animals, identical with that of our controls. One hundred and ninety-seven young survived, or 36.2 per cent as compared with 37.8 per cent of the controls. Growth was slow but development rapid. The ears opened from the second to the third day, an average of 2.8 days. The incisors erupted from the seventh to the eleventh day, an average of nine days. The animals were covered with a fine downy fur from the sixth to the seventeenth day, an approximate average of the twelfth day. The eyes opened from the twelfth to the sixteenth day, an average of 13.8 days. The testes descended from the sixth to the twenty-sixth day, an average of 15 days, as compared with 31 to 40 days for the controls. The vagina opened from the thirtieth to the thirty-ninth day, an average of 37 days.

The birth weight in this group was somewhat under that in the second generation and growth was much more retarded. At 10 days the pineal animals lagged by nearly 40 per cent and at 30 days more than 50 per cent. Thus the average pineal rat at one month was less than half the normal size and weight. (Figure 5.)

The Rate of Growth and Development in the Fourth (F_3) Generation. The fourth generation consisted in all of 155 animals born in 24 litters to nine pairs of rats treated with pineal extract. The parents, grandparents

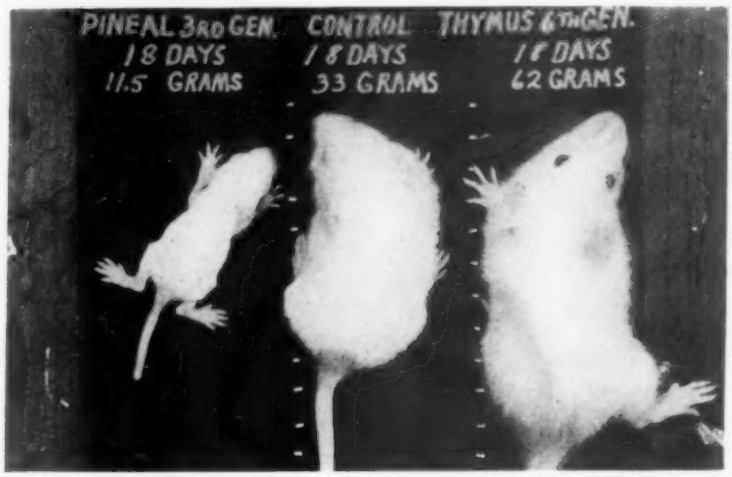

FIG. 5. For purposes of comparison the sixth generation thymus rat was included.

and great grandparents had all received injections of pineal extract (Hanson). The interval between casting litters was an average of 27.8 days. The average litter consisted of 6.4 animals with an average birth weight of 4.3 gm. The mortality was high; only 30 per cent of the young survived. In this generation growth was still further retarded while development was still further accelerated. The ears opened in two to three days, an average of 2.3 days. The teeth erupted from the fifth to the eighth day, an average of 6.9 days. Hair appeared between the fifth and the twelfth day, an average of nine days. The eyes opened at five to 13 days, an average of nine days. The testes descended at five to 12 days, an average of 10 days, and the vagina opened at 29 to 39 days, an average of 32 days.

The Rate of Growth and Development of the Fifth (F_4) Generation. The fifth generation consisted of 12 rats born in one litter, the birth weight varying from 3.8 to 4.5 gm., an average of 4.2 gm. The two smallest animals succumbed at five days without showing any increase in weight. Ten animals survived for two weeks and only five are living at 30 days. In this group, growth was still further delayed and development still further accelerated. The ears opened on the first to third day. The teeth erupted from the third to the fifth day. Hair appeared from the fourth to the eighth day, was scanty in amount, downy in consistency, the pelt being poor as compared with that of our thymus test strain. The rats opened their eyes between the fourth and the eighth day. The testes descended between the fourth and the ninth day and the vagina opened at an average of 24 days. (Figure 6.)

In this generation growth is still further restricted. The weight curve falls below that of the F_3 generation. To attain greater accuracy, we have based this curve on six litters, five of which have been observed since April

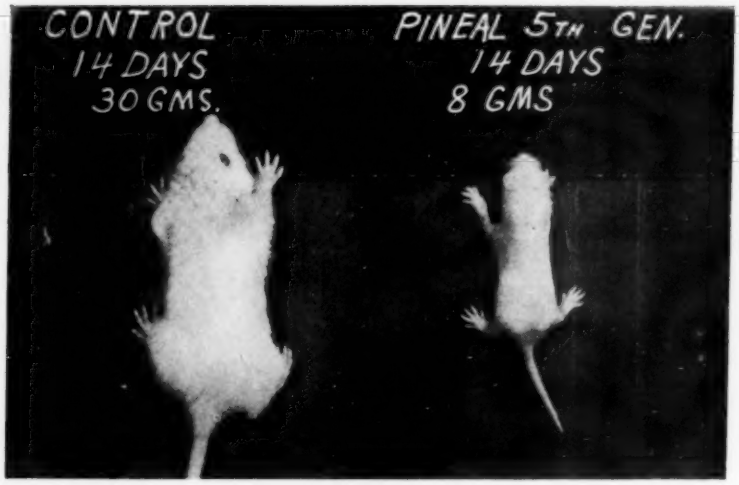

FIG. 6.

16, the closing date for the work as a whole. The rats of the fifth generation weighed 50 per cent of normal at 10 days and those surviving to the thirtieth day weighed but 40 per cent of normal.

General Discussion of the Rate of Growth and Development of Rats under Treatment with Pineal Extract. To date five generations of the pineal strain of rats have been under observation. An analysis of the biological data of each of these generations reveals several significant facts. In the first (F_0) generation no effect is apparent other than a moderate loss of weight, phenomena suggestive of sex excitation or increased size of penis and early breeding. In the second (F_1) generation there is definite retardation in growth with mild precocity in gonadal development. In the subsequent generations, the third to the fifth, there is accruing retardation in growth with accruing acceleration in gonadal and bodily development.

As a result of these changes, the young are quite bizarre in appearance, especially in the second and third weeks until the body is thickly covered with fur. The configuration of the body as well as the shape of the head and the face seem to depart considerably from normal. The short snout, broad face, round head, heavy jowl and bulging eyes give a " bull dog " appearance. The small size, the large feet, the squat, compact figure suggest the " Hercules in miniature " effect said by some to characterize the clinical picture of pineal tumor.

These animals we have referred to as " dwarfs." In this early period the stunting in growth is accompanied by disproportions in bodily development. Later, however, after the first month the animals appear small and

delicate but like normal rats in miniature. Still later, after 100 to 200 days, these rats appear somewhat small but normal in appearance but on examination the fur is found to be unusually long and thick and on weighing the animal it is found to be only 50 to 60 per cent of the weight of the control.

It is of decided interest that the effect on gonadal development appears earlier than that on bodily development. It is quite marked in the second (F_1) generation whereas the precocity in bodily development does not appear until the third (F_2) generation.

Lack of uniformity in size and in the rate of growth and development is striking. Even in a single litter variation is marked. Because of this variability, the range of values as well as the average is presented in the following table. (Table 3.)

TABLE III

Progressive Development under Pineal Treatment

	Ears Opd.	Teeth Erupt.	Fur Appd.	Eyes Opd.	Testes Descd.	Vagina Opd.
Controls	2½–3½ (3)	8–10 (9.0)	16 16	14–17 (15.5)	31–40 38	55–72 65
F_1	2–3 (3.3)	8–10 (9.0)	7–16 (13.0)	12–17 (14.9)	12–36 (22.0)	32–56 (45.0)
F_2	2–3 (2.8)	7–11 (9.0)	6–17 (12.0)	12–16 (13.8)	6–26 (15.0)	30–39 (37.0)
F_3	2–3 (2.3)	5–8 (6.9)	5–12 (9.0)	5–13 (9.8)	5–12 (10.0)	29–39 (32.0)
F_4	1–3 (2.0)	3–5 (4.0)	4–8 (5.0)	4–8 (6.0)	4–9 (5.0)	23–26 (24.0)

The data on growth and development when tabulated or expressed in curves reveal the same step-like progression in succeeding generations under treatment which was evidenced in our thymus work. However, in the pineal studies there appears a peculiar paradox, a dissociation of the effects on growth and development.* The progressive effect is in two or possibly three directions, retardation in growth accompanied by acceleration in gonadal development and also in bodily development.

The effect of pineal extract on growth is revealed in figure 7, which represents the growth curves of the successive generations.† The "dwarf-

* This suggests that more than a single agent or substance is concerned in the process of growth and development. Several factors may contribute to this "dwarfism": (1) Loss of weight seen in the F_0 group; (2) retardation of growth by direct effect; and (3) inhibition of growth secondary to gonadal maturity. In view of the latter some may not regard the combination of retarded growth with accelerated development as a paradox.

† The closing date for these studies was April 16. At that time we had one litter of 12 in the fifth generation on which to base the curve for F_4. It seemed wise to include additional data up to July 4 for both the curves for F_3 and F_4. F_3 is therefore based on 30 litters and F_4 on 5 litters.

ism" resulting from pineal extract (Hanson) is usually permanent, though less striking as the animals age. In rats of the second or later generations perhaps less than 10 per cent attained normal weight or growth. The early

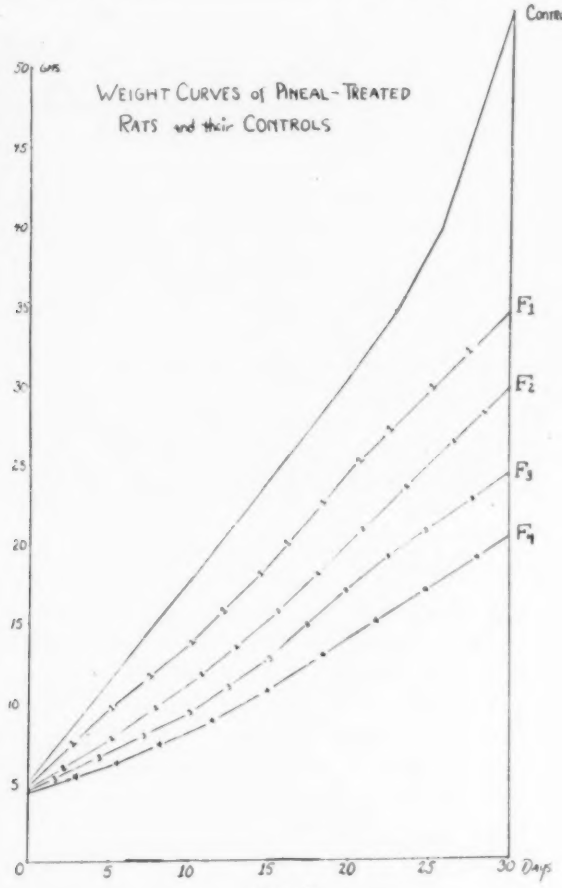

FIG. 7.

employment of potent extract in the young almost always insures more striking and more permanent effects.

In summary it may be said that on the physical side the biological effect of administering pineal extract (Hanson) is "dwarfism" associated with acceleration of gonadal and bodily development.* It would appear, therefore, that the rats in our third and succeeding generations under pineal treatment in some ways suggest the clinical picture, macrogenitosomia precox, seen in pineal tumor although our animals do not pass through a period of early accelerated growth sometimes encountered in the clinical condition.

* Caution must be exercised in arguing from this statement that a function of the pineal gland is to retard growth and accelerate differentiation since experiments now being carried on in this laboratory by Dr. N. H. Einhorn indicate that pinealectomy also retards growth and is associated with accelerated development.

Other Biological Effects. In addition to the effects of pineal extract on the rate of growth and development, certain other considerations appear worthy of presentation. These have to do with activity and behaviorism, time of weaning and the frequency of blindness.

Activity and Behaviorism of Rats under the Influence of Pineal Extract (Hanson). Most of the pineal treated rats appear fairly healthy and their actions asleep or awake resemble grossly those of normal controls although they seem more somnolent or lethargic. However, they are distinctly more irritable than normal. They resent needle puncture though they apparently suffer no undue pain or distress following the injection of pineal extract.

The mother instinct is quite variable, in some instances complete neglect, in others undue apprehension and combativeness to all who even approach the young. At times gloves have been essential in handling pineal mothers when a litter was in the cage, the same animals at other times being friendly and docile.

The young pineal "dwarfs" tend to lie on their side in a curled up position in the first days of life. At this time they are relatively inactive. At the end of the first week, after their eyes have opened they appear weak and have difficulty in getting about the cage. Not until they are 15 to 20 days of age will they attempt to climb the side of the cage or to escape from a small wire net enclosure. Their activity during these early days is decidedly below normal as is their strength.

Weaning. Weaning in the early days of life is impossible in the pineal test strain. Even under the best conditions the animals are very small and most of them too weak to wean even at 20 to 23 days of age. When a subsequent litter has arrived in the course of 23 to 25 days, we have found some difficulty in the enforced weaning of the young of the preceding litter. Weaning should be attempted preferably about the thirtieth day.

Swimming. Because of their apparent inactivity and helplessness, it was considered inadvisable to immerse very young pineal test rats. However, it has been found that the best developed pineal rats of the fourth and fifth generations can swim at 20 days, most of them, however, not until the thirtieth day.

Eye Anomalies. Blindness is of rather frequent occurrence. This has been observed in perhaps a dozen rats in the pineal group but only twice in our thymus strain. As a rule blindness affects one eye but in four instances it has been bilateral. The cause is unknown. It is possible that injury plays a rôle. Bilateral cataracts were responsible in two rats. Two instances of congenital hypertrophy of the eye have been noted [2] and some instances of the so-called pineal eye.

The opening of the eye is peculiar at times. When the eyelids separate the pupil is not revealed, the slit being too high for the pupil. Eventually, however, some form of adjustment is effected, whereby the eyeball and palpebral fissure appear to harmonize.

CONCLUSIONS

1. Thymus extract (Hanson) has accelerated the rate of growth and development and has hastened the onset of adolescence in the offspring of treated rats.

2. Thymectomy in parent rats has retarded the rate of growth in the young as indicated in the weight curves.

3. Pineal extract (Hanson) has retarded the rate of growth and accelerated the rate of development and has hastened the onset of adolescence in the offspring of treated rats.

4. The injection of succeeding generations of parent rats has resulted in the amplification of the effects of thymus and pineal extracts (Hanson).

We wish to acknowledge our indebtedness and gratitude to Dr. H. H. Donaldson of the Wistar Institute for his kindly interest, unfaltering faith and invaluable counsel.

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ARTIFICIAL PNEUMOTHORAX IN THE TREATMENT OF LOBAR PNEUMONIA * †

By BENJAMIN BURBANK, M.D., and EMIL ROTHSTEIN, M.D.,
Brooklyn, New York

DURING the past year, a number of reports [1, 2, 3] have been published of effects secured in the therapy of lobar pneumonia by the use of artificial pneumothorax. We present here a report of 20 cases of lobar pneumonia treated by artificial pneumothorax, with a resulting mortality of 10 per cent. We realize that no permanent conclusions can be reached from such a small series, but we feel that until larger and more carefully controlled groups of cases have been reported it is important to make available all data bearing upon the effect of this mode of treatment. We wish also to present certain views of our own as to the rationale of this therapeutic procedure.

Selection of Cases. We have treated, in this series, 20 cases, selected only by the indications and contraindications stated below. The total number of cases which were available made it seem inadvisable to treat alternate cases, as we then would have had an insufficient number of treated cases. We have no controls; the only cases with which any comparison could be made are seven patients in whom the proper indications existed but no free pleural space could be found, or a pleural effusion was present. Similarly, because of the small number of cases treated, we feel it unnecessary to compare the statistical results with those for the hospital as a whole in previous years. There can be no doubt that if in a much larger series, including all or any types of pneumococci, a mortality of 10 per cent were not exceeded this would represent a marked improvement in pneumonia mortality statistics, especially for a city hospital of the nature of Kings County Hospital, receiving as it does, the indigent, the overexposed and the alcoholics.

The essential data on our 20 cases are given in table 1. We have selected four case abstracts to illustrate the varying therapeutic effects:

CASE REPORTS

Case 3. N. W., Jewish male, age 42, was admitted on October 28, 1934. He had been taken ill with pneumonia on the day before admission. On examination he was found acutely ill; his general condition was poor; temperature 104° F. with proportionately elevated pulse and respirations. Dyspnea was well marked with rapid shallow respirations due to marked chest pain. There was evidence of complete consolidation of the right lower lobe. No complications were present. Pneumothorax was started October 29, with 350 c.c. of air, followed that afternoon by 350 c.c. more, and by 300 c.c. the following morning, the final pressure going to plus 4 cm. of

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From the Services of Drs. B. A. Fedde, H. Feinblatt, and J. G. Terrence, Department of Medicine, Kings County Hospital, Brooklyn, N. Y.

† We are deeply indebted for the advice and assistance of Drs. Fedde, Feinblatt and Terrence, and for the permission to report these cases from their services, of which they are, respectively, the Attending Physicians.

TABLE I

Treatment of Pneumonia by Artificial Pneumothorax

Case	Sex	Race	Age	Result	Day of first treatment	Condition at start of treatment	Total amt. air injected	Day of disease when temp. first reached normal	Complications before treatment	Complications after treatment
1	f.	col.	28	recov.	3	fair	1,600 c.c.	7th	pregnancy	none
2	m.	col.	37	died	4	poor	1,000 c.c.	died	chr. alcoholism, luetic aortitis	delirium tremens
3	m.	w.	42	recov.	3	poor	1,000 c.c.	4th	none	none
4	m.	w.	28	recov.	5	poor	800 c.c.	—	none	bilateral parotitis
5	m.	col.	45	recov.	4	fair	750 c.c.	—	arterioscl. cardiovasc. dis.	empyema: auricular fibrill. and flutter
6	m.	w.	32	recov.	4	fair	900 c.c.	6th	aortic regurgitation	none
7	m.	col.	32	recov.	2	fair	800 c.c.	—	none	empyema
8	m.	w.	34	recov.	6	fair	1,050 c.c.	7th	none	none
9	m.	col.	25	recov.	6	fair	1,350 c.c.	8th	none	none
10	m.	w.	27	recov.	3	poor	900 c.c.	7th	none	contralateral spread to r.l.l.
11	m.	col.	25	recov.	5	poor	600 c.c.	7th	none	none
12	m.	col.	50	recov.	5	poor	900 c.c.	7th	none	none
13	m.	w.	52	died	3	poor	500 c.c.	died	none	contralat. spread to entire left lung
14	m.	w.	53	recov.	4	bad	800 c.c.	8th	none	none
15	m.	w.	25	recov.	2	poor	1,000 c.c.	7th	none	none
16	m.	w.	49	recov.	4	poor	1,000 c.c.	10th	none	carbuncles
17	m.	w.	44	recov.	5	fair	1,000 c.c.	7th	none	none
18	m.	col.	25	recov.	4	fair	1,000 c.c.	5th	none	none
19	m.	w.	62	recov.	3	poor	600 c.c.	8th	none	none
20	m.	col.	42	recov.	1	poor	700 c.c.	3rd	congenital heart disease	none

water. The immediate effect was an increase in pain; this lasted for 20 minutes and then was followed by complete and permanent relief of pain. The patient became much more comfortable and slept peacefully through the afternoon and the following night. He was able to breathe deeply and cough without pain. On the afternoon of October 30 (the middle of the fourth day) the temperature dropped to 99° and remained normal from then on.

Case 2. P. W., negro male, age 37, was admitted July 2, 1934. The onset of his pneumonia had been on June 29, 1934. On admission his examination showed that he was acutely ill and in poor general condition. His temperature was 103° F., and there was a proportionate rise in pulse rate and in respirations. Dyspnea was well marked with rapid shallow respirations due to moderate chest pain. The lung involvement found consisted of complete consolidation of all three lobes of the right lung. In this patient certain complications were present: luetic aortitis (asymptomatic and found at postmortem), and chronic alcoholism. The first pneumothorax treatment (300 c.c.) and the second (400 c.c.) were given on the day of admission and the third treatment (300 c.c.) on the day following, July 3. The final pressure was plus 2 cm. of water. Immediately after the first treatment the patient had complete and permanent relief of pain. A few hours after the first treatment he showed evidence of beginning delirium; four hours after the second, a full-blown delirium tremens was present, requiring sedation and restraints. In addition to pneumothorax, he received oxygen inhalations, and intravenous glucose. Death occurred on July 3, 1934. Autopsy revealed consolidation of the entire right lung, cerebral edema and luetic aortitis.

Case 4. T. L., Greek, male, age 28, was admitted November 3, 1934, on the fifth day of his pneumonia. On examination he was found acutely ill, but his general condition was fair. His temperature was 103° F., with commensurate increase of the

pulse and respirations. Dyspnea was moderate, with moderate chest pain. The lung involvement found consisted of consolidation of the left lower lobe. No complications were present. Pneumothorax was started November 4 with 400 c.c.; on November 5,400 c.c. more were given. Immediate and complete relief of pain was obtained

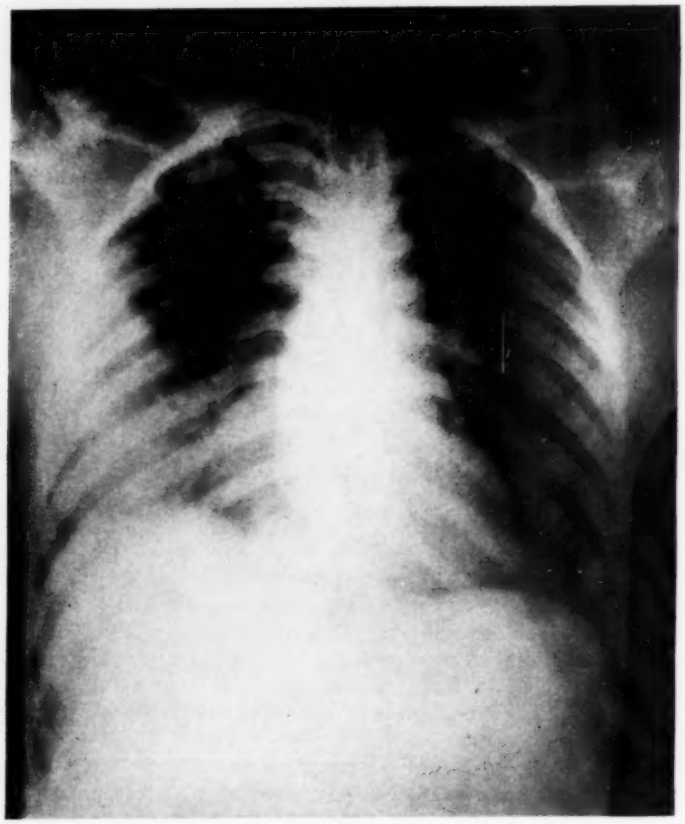

FIG. 1. *Case 3.* Plate taken on admission; complete consolidation of the right lower lobe.

and he was able to breathe, cough, and sleep without difficulty. That afternoon, consolidation of the right lower lobe was discovered; the general condition became poor and required the use of an oxygen tent and intravenous glucose. When his pneumonia was just beginning to resolve he developed bilateral parotitis; that on the left side required incision and drainage. He was discharged as recovered on December 20. It is of interest to note that the left side was completely resolved and aerated within three weeks of the onset, while the right, untreated, took six to seven weeks to become completely resolved (as determined by roentgen-ray).

Case 20. G. D., negro male, age 42, was admitted December 27, 1934. There was a history of some heart condition since the age of two. The onset of his pneumonia was on the day of admission. The examination on admission showed that he was acutely ill but without pain or dyspnea. His heart was enlarged and there was a loud systolic basal murmur. There was no apparent cyanosis and no other evidence of past or present decompensation. This cardiac condition was interpreted as due to congenital heart disease. The roentgen-ray of the heart revealed enlargement and

marked prominence of the pulmonary conus. Examination of the lungs showed complete consolidation of the left lower lobe. Pneumothorax was started on December 28, 1934 (20 hours after the onset). At the first treatment 300 c.c. were given, and the same afternoon 400 c.c. more, the final pressure going to plus eight cm. of water. There was no notable symptomatic effect. The temperature dropped to

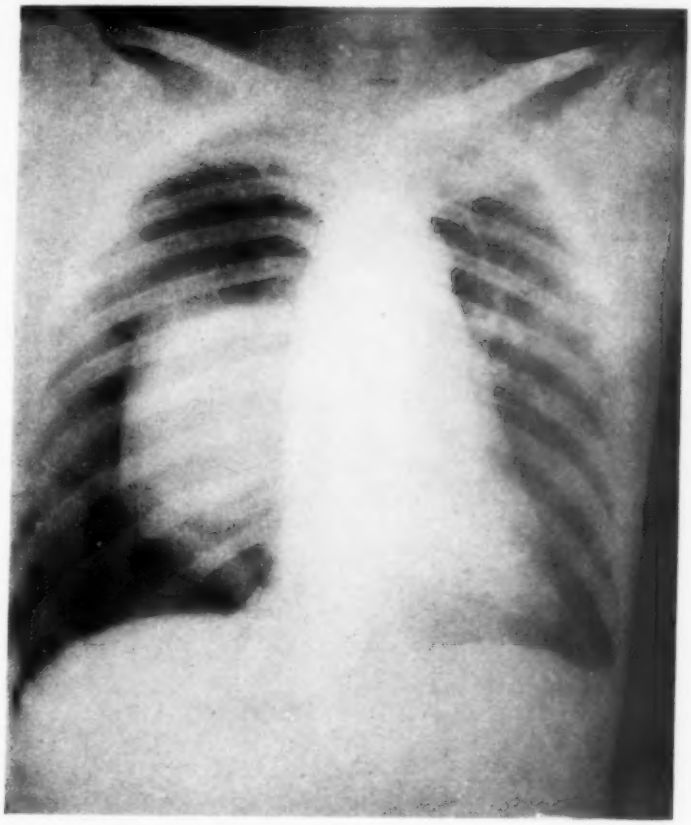

FIG. 2. *Case 3.* After the introduction of 1000 c.c. Air is seen between the involved portion of the right lung and the chest wall, and the lung and the diaphragm. The upper portion of the right lung is adherent.

normal on the afternoon of December 29, i.e. 50 hours after the onset of the disease, and remained normal. This is the only case in which the early crisis may be attributed to the treatment. This may be related to the early start of the treatment in this case.

Indications and Contraindications. In the present state of our knowledge it is only possible to define indications and contraindications tentatively. For the present we have set for ourselves certain arbitrary indications with the realization that as time goes on they may become either more elastic or more rigid. With these reservations we list the indications that have guided us in this series.

1. The pneumonia must be of the lobar type.
2. The lung involvement must be unilateral.
3. The age of the patient must be below sixty.
4. Moribund patients must be excluded.
5. The patient must be actively febrile.
6. The stage of the disease must be earlier than the sixth day.
7. Pleural effusion must not be present.
8. Complications already present must be considered.

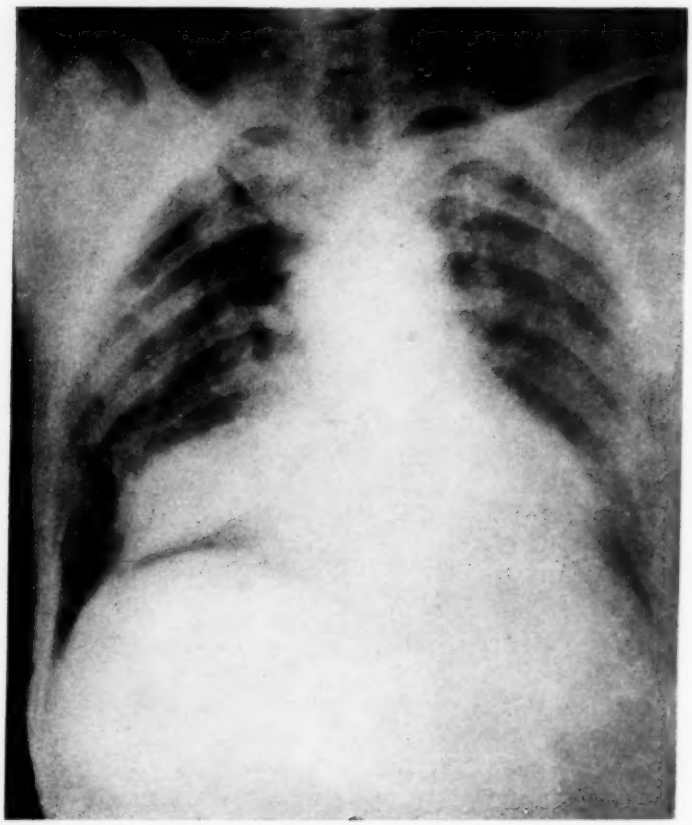

FIG. 3. *Case 2.* Plate taken after the introduction of 1600 c.c. of air. The total amount of consolidated lung is unchanged. The apparent collapse is due to two factors: (*a*) the cardiac displacement; (*b*) collapse of the uninvolved portion of the right lung.

Lobar Pneumonia. Because of certain pathological features, chiefly pleural involvement and a tendency to be unilateral, as well as the tendency to run a short and acute course, lobar pneumonia is more suitable for pneumothorax treatment than is bronchopneumonia. To date we have treated only cases of lobar pneumonia.

Unilateral Lesion. All our cases were selected as unilateral; in some, physical signs were misleading, and roentgen-ray evidence was relied upon. After pneumothorax was started, three cases developed lobar contralateral

lesions; one of these died and two recovered. In addition, in several cases small infiltrative patches were seen on the roentgen-ray, on the previously unaffected side, with neither signs nor symptoms, nor noticeable effect upon the course. Although no bilateral cases were treated deliberately, from our experience to date it does not seem likely that any ill effects would ensue,

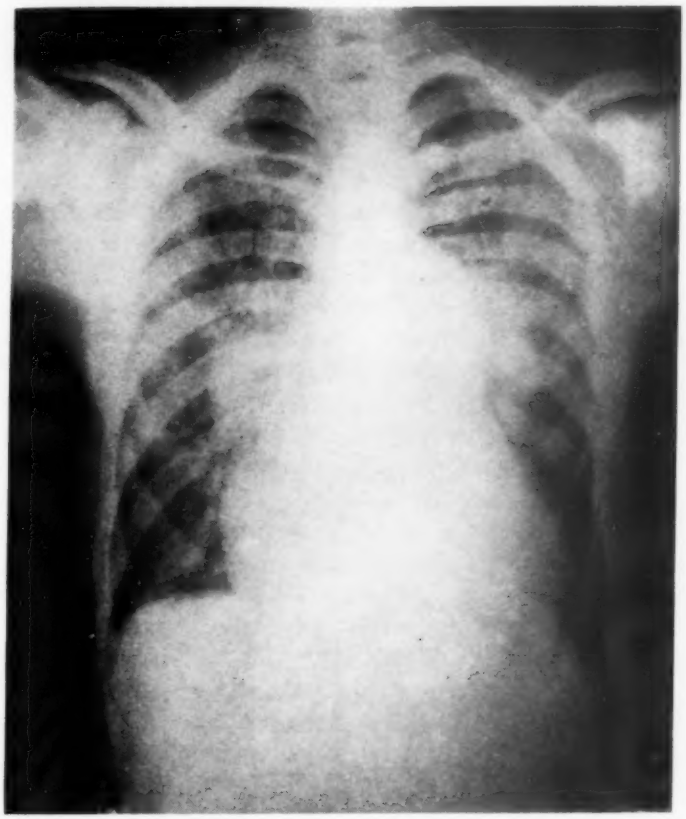

FIG. 4. *Case 20.* This illustrates the congenital heart condition. A small area of pneumothorax is seen in the left lower lung field. The left lung is almost completely resolved. A small patch of pneumonic involvement is seen in the right mid-field.

if this treatment were cautiously used, in a bilateral lobar pneumonia, especially in the presence of severe pleuritic pain. Of our cases, at the onset of treatment, nine had consolidation of the left lower lobe, four of the right lower lobe, two of the right lower and middle lobes, two of the entire right lung and one each of the right upper lobe, of the right middle and upper lobes, and of both lobes of the left lung.

Age. The principal factor to be considered here is the function of the lungs, as affected by the presence of emphysema and chronic bronchitis. These pulmonary conditions increase with increasing age. We have arbitrarily set 60 years as the upper limit, but we pay less attention to the

chronological age than to the presence of diminished breath sounds, fixed barrel chest, numerous rhonchi, and a past history of dyspnea upon slight exertion. In the absence of these factors we would at present not hesitate to treat a patient above the age of 60 (as in our case 19). With such patients it is advisable to give small amounts of air, and cautiously. Of our cases, six were in the third decade, four in the fourth, six in the fifth, three in the sixth, and one in the seventh (62), with an average age of 40 years.

General Condition. Moribund patients no longer would respond to pneumothorax, because this form of treatment does not directly affect the immunologic balance. One case which we attempted, but in which there was no free pleural space, died 16 hours after the attempt at pneumothorax. The general condition of our patients on the day of treatment was estimated as fair in eight cases, poor in eleven, and bad in one.

Fever. For proper evaluation of statistical results no cases should be treated unless acutely ill and febrile, because otherwise cases will be included after the crisis with signs of consolidation still present, thus falsely increasing the percentage of recoveries. From a therapeutic standpoint there is probably no contraindication. All our cases were actively febrile (temperatures of over 102° when treatment was started).

Day of Illness. Cases febrile past the sixth day are not suitable for treatment while pneumothorax is still in the experimental phase, as a large percentage of such cases if uncomplicated will recover. From a therapeutic standpoint there is probably no contraindication, and indeed, pneumothorax may be indicated if there is definite evidence of prolongation of the fever due to lobar contralateral extension. Of our series, treatment was started during the first day in one case, the second day in two, the third day in six, the fourth day in five, the fifth day in four, and the sixth day in two; an average of three and one-half days.

Pleural Effusion. From a therapeutic standpoint, cases with small effusions probably do not offer any contraindications, but until the percentage of empyemas with pneumothorax treatment is established it would not be wise to treat cases with this complicating factor.

Complications already Present. At the start several of our patients had various complications. Our first patient was pregnant (two months). Our second patient was a chronic alcoholic; this condition progressed to delirium tremens and proved to be a fatal complication. This patient had also (as shown at autopsy) luetic aortitis. Our fifth patient (52 years old) had arteriosclerotic heart disease; and during the course of the pneumonia he developed auricular fibrillation followed by auricular flutter (EKG); clinically we also found partial block and pulsus alternans. Our sixth patient presented a cardiac condition, with signs of aortic regurgitation, but without cardiac enlargement, or any signs of past or present decompensation. The Wassermann was negative. Our twentieth case presented a congenital cardiac condition, probably tetralogy of Fallot (loud systolic rumble over

the pulmonic area, cardiac enlargement, marked enlargement of the pulmonary conus in the roentgen-ray, no cyanosis or evidence of past or present decompensation, history of heart disease since the age of two). None of these complications was thought to be sufficient to contraindicate the use of pneumothorax, and the outcome of these cases bore out this opinion.

Method of Treatment. Our selection of cases was guided by the indications and contraindications discussed above. We found it advisable in doubtful cases to take a roentgen-ray, before treatment.

The apparatus utilized was the standard pneumothorax machine, with 18–20 gage needles; no special needles were used. When feasible, the site of puncture was selected over one of the uninvolved lobes. Novocaine anesthesia was used. Air was never introduced until the fluctuations obtained were characteristic of intrapleural pressures. Readings were taken frequently to avoid sudden pressure rises. The amounts introduced in our cases varied from 200 to 500 c.c. for one treatment and a total of 600 to 1600 c.c. At present we feel that the ideal amount is about 1000 c.c., divided into two treatments of 500 c.c. each, at a four to six hour interval. Most of the patients were benefited greatly by the first 500 c.c., and none of those receiving over 1000 c.c. were noticeably harmed.

Pressure Readings and Amounts. The initial readings found will vary, but the average is slightly less negative than in the normal chest; assuming the normal to be — 10 to — 6 cm. H_2O, our cases average about — 6 to — 2 cm. Two or three cases had higher negative readings (— 14, — 10) and others less negative (— 4, 0). In all cases, after 500 to 1000 c.c., the pressure rose much more than in normal or slightly diseased lungs (as in tuberculosis). Arbitrarily we set as the limit of positive pressure, plus 10 cm. of water, although we prefer, if possible, not to reach such pressures. When the pressures rise rapidly, we prefer to divide the course of treatments into doses of 250 to 300 c.c., rather than 500 c.c. However, there was no discernible relationship between the degree of comfort, dyspnea or relief of pain and negativity or positivity of the intrapleural pressures. Therefore we are much less reluctant to go to pressures of plus 6 or plus 8 if necessary, than when we first started this series of cases.

Clinical Effects. These may be divided into immediate and delayed. *Immediate effects:* None of our cases presented any immediate pain, shock or discomfort. Upon introduction of the air the immediate effect depends largely upon the previous symptoms. In the presence of severe pleural pain, the relief is immediate and almost complete, occurring while the air is still being administered. The patient is changed from one who is in pain, breathing with short jerky respirations, to one who is comfortable and without pain, and who can breathe and cough freely. The subjective relief in these cases is most gratifying. In several cases the patient, having been awake most of the previous night due to pain, fell asleep a few minutes after the completion of the first treatment. In six cases the treatment caused a small bout of coughing, lasting from three to five minutes. Four patients

who had no pain before the treatment complained of pain for 10 to 15 minutes afterwards. In no case did this pain last longer, and in all was followed by complete relief of pain. *Delayed effects:* (1) Relief of pain is permanent, usually after 500 c.c. Relief after the first treatment occurred in 10 cases, after the second treatment in six more, and four had no pain at any time. (2) The effect upon cough: The patient is able to cough freely and without pain; the amount of sputum is increased at first due to the free painless coughing; during the rest of the illness the sputum is apparently less tenacious. (3) The effect upon sleep and rest: The patient is able to sleep and rest without opiates. (4) Distention: None of our 20 patients developed abdominal distention. This is probably directly related to the therapy, and not coincidental, as many of our patients who appeared very toxic were free of this frequent and distressing symptom. (5) Effect upon toxicity: No direct effect was observed. (6) Early crisis: Only two of our cases had a crisis before the fifth day after the onset of the pneumonia (one on the fourth and one on the second day (48–50 hours). This is different from the experience of the few other physicians who have thus far reported their results with artificial pneumothorax.

Complications. These may be divided into immediate and delayed. *Immediate:* There were no immediate complications, such as pleural shock, air embolism or increase in dyspnea or cyanosis. *Delayed:* (*a*) Pleural adhesions: Out of 27 cases tried, seven had such diffuse pleural adhesions that either no free space was found or only 75 to 100 c.c. of air could be introduced with pressures going up to + 10. In these cases pneumothorax was discontinued, and they were considered as not having been treated with pneumothorax. Partial adhesions were present in several cases, frequently over the uninvolved areas. There was no appreciable effect in lessening the efficiency of the pneumothorax, but there were observed somewhat higher pressures than in the other cases. (*b*) Empyema: Of our 20 cases, two developed empyema. Both were operated upon (rib resection and open thoracotomy) and are gradually recovering. Both were due to *Streptococcus hemolyticus.* The suggestion has been made that those empyemas which would complicate pneumonias with pneumothorax might be expected to be more severe and to have long drawn out courses, because of the effect of the pneumothorax in preventing early encapsulation and localization of the infections. The two patients who developed empyema in our series have been in hands of the surgeons for two and one-half to three months. Whether this will be a constant factor cannot be determined as yet. It is not mentioned in the literature. From a purely hypothetical standpoint one would expect the incidence of empyemas to decrease, as the air removes to a large extent the irritating friction between the two acutely inflamed layers of the pleura. (*c*) Delayed pulmonary changes: Atelectasis and pulmonary fibrosis have not been observed in any case, the lung being completely expanded in every case before discharge. This absorption takes from two to three weeks. In two cases in which spread to the other side

occurred with later recovery, the lung on the side of the pneumothorax showed much earlier and more complete resolution (roentgenologically) than the other. (*d*) Delirium developed in five cases; in three it required restraint. (*e*) Other complications: Delirium tremens developed in one case of chronic alcoholism. This patient died. Our fourth case developed bilateral parotitis, one side requiring incision and drainage. Our fifth case developed auricular fibrillation and auricular flutter, on the basis of a previously existing arteriosclerotic heart disease. After a period of seven to ten days during which he was critically ill, he recovered a normal sinus rhythm; he received digitalis, sedation and intravenous glucose. This patient also was one of the two who developed empyema. Our sixteenth case developed several carbuncles over the sacrum but recovered. (*f*) Three cases developed contralateral lobar pneumonia; one of these died.

Results. Out of the 20 cases, 90 per cent recovered. The mortality in any large group of pneumonias, including all ages, complications and pneumococcus types, ranges considerably over 10 per cent, especially in a hospital of the nature of the Kings County Hospital. Although a series of 20 cases is too small for definite conclusions, the mortality of 10 per cent in a series treated from the end of October through December and including nine negroes, is very suggestive. In seven cases pneumothorax was tried but no air could be given because of pleural adhesions or effusion. Of these, four died, and four developed empyema (including two of the fatal cases).

Rationale of Therapy. From our observations of these cases we have come to the following conclusions: The beneficial effects of pneumothorax are apparently related only to the relief of pleural irritation. There is practically no collapse as seen on the roentgen-ray of the involved lobe and no noticeable effect upon toxicity, nor is it reasonable to assume a diminution of blood or lymph drainage from the involved areas. The rationale of the therapeutic effect appears to us to be as follows: (*a*) Effect upon respirations: Respiration becomes free, painless and of increased depth. This lessens the exertions of the patient, lessens the cyanosis and anoxemia, and lessens the chance of contralateral diminished aeration with atelectasis and secondary pneumonic involvement. (*b*) Relief of pain: This allows the patient to rest comfortably; sleep is made possible without the use of opiates. (*c*) Effect upon cough: Cough is made almost painless in a large majority of the cases; and productive cough insures proper drainage from the diseased area, and also makes much less likely the development of bronchial obstruction in the healthy lobes of the diseased lung or of the opposite healthy lung. Such bronchial obstruction with tenacious sputum tends to secondary pneumonic spread. (*d*) Effect upon distention: None of our cases developed abdominal distention. Inasmuch as this was not apparently related to the lessening of toxicity, we feel that a large part in the development of this troublesome symptom is played by diaphragmatic pleurisy. Roentgen-ray studies showed air between the lung and the

diaphragm in almost all cases, and the relief thus afforded at this point is, we feel, directly connected with the absence of distention.

Roentgen-Ray Findings. All cases were roentgen-rayed at some time in the course of their stay in the hospital and in almost all cases there were several roentgenograms. Only one showed unquestionable collapse of the diseased area. In the other cases, when collapse of the consolidated area was suggested by the film, it could be explained by one of three factors: (1) Displacement of the mediastinum, or of the lung into the mediastinum; (2) Collapse of that portion of the lobe which was not completely consolidated; (3) Taking of the film after resolution had begun. The typical picture showed a layer of air (about 1 cm. in width) between the consolidated lung and chest wall, and between the diaphragm and the lung, in lower lobe lesions. The air tended to have a selective location over the diseased, rather than over the healthy, lobes. The air was apparently absorbed by the end of 10 to 14 days. A small amount of fluid was commonly seen in the costophrenic sulcus (in about 50 per cent of the cases).

Comparison with Other Forms of Treatment. We do not wish to indicate it as our belief that pneumothorax is meant to replace other accepted forms of treatment, such as serum, oxygen, intravenous glucose, and careful routine nursing and medical care. These forms of treatment should be combined according to the indications and contraindications for each. In this series no serum was used, but oxygen was administered in two of the non-fatal cases, as well as in both of the fatal ones, the indication being the presence of more than the faintest discernible trace of cyanosis. Similarly intravenous glucose (50 c.c. of 50 per cent solution every four hours, for from two to four injections) was administered to six cases, the indication being a drop of blood pressure below 100 systolic.

In comparison with serum, pneumothorax presents certain obvious advantages and disadvantages. Pneumothorax requires no typing; it can be used at once; it is not limited by the pneumococcus type; there is no danger of anaphylaxis. It has also the advantage of being inexpensive. It requires, however, special apparatus and special technical experience. On the other hand, the use of serum is not restricted by age; it can be used in bilateral cases; it is specific; it can be administered by one who has very little experience in such a form of treatment. It is often prohibited, however, by lack of facilities for typing; by the lack of serum for the specific type of pneumococcus; or by economic difficulties. It seems apparent that these modes of treatment are supplementary to each other.

Summary

Twenty cases of lobar pneumonia treated by artificial pneumothorax are reported, with a mortality of 10 per cent. The indications, contraindications, details of treatment, clinical effects, complications, and rationale of pneumothorax treatment are discussed. We believe that artificial pneumo-

thorax is a beneficial method of treatment in lobar pneumonia and should be given more extensive trial.

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IMMUNOLOGICAL APPLICATIONS OF PLACENTAL EXTRACTS; EFFECTIVENESS BY ORAL ADMINISTRATION * †

By C. F. McKhann, A. A. Green, L. E. Eckles, and J. A. V. Davies,
Boston, Massachusetts

A number of investigators have found that the umbilical cord blood of infants contains certain antibodies in amounts commensurate with those in the maternal blood stream.[1] This would indicate that the immunity of the newborn infant to some of the infectious diseases is derived in part by placental transmission of antibodies from the mother. Protein extracts composed of the globulins derived from the human placenta and the blood contained in it have been prepared and have been demonstrated to contain diphtheria and scarlet fever antitoxins, and antibodies which neutralize poliomyelitis virus and protect exposed, susceptible children against measles.[2]

In the present communication we desire, first, to review the progress which has been made in studies to determine the practicability of immunological application of placental extracts, particularly in the prevention and modification of measles, and second, to report investigations which indicate that the immune bodies of placental extracts may be effective following oral administration. The tests of the material following oral administration have been made largely by the determination of immunity to scarlet fever as measured by the Dick test.

Distribution of Antibodies in Fractions of Placental Extracts

In the preparation of placental extracts, normal placentas from non-syphilitic and non-toxic mothers were collected in sterile containers and were pooled in lots of eight to 50 placentas. The organs were ground in a meat chopper and extracted with 4 per cent salt solution. The saline extracts contained fetal blood, placental tissue proteins, and some maternal blood. After the saline extracts had been centrifugated to free them of blood cells and tissue débris, the globulins were separated by precipitation with half saturated ammonium sulphate. The ammonium sulphate was removed by dialysis. The preparations so made contained antibodies in considerable concentrations, but the material was in turbid suspension and could not be passed through Berkefeld filters. Subsequently a separation of the extracts into fractions was made and the association of antibodies with the various globulins was sought, in order to find, if possible, fractions useful clinically

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From the Department of Pediatrics, Harvard Medical School, the Department of Communicable Diseases, Harvard School of Public Health, and the Infants' and Children's Hospitals, Boston, Mass.

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which could be passed through Berkefeld or Seitz filters. Also, a series of tests was made to ascertain roughly what proportion of the protein represented blood serum and what was derived from the tissues. In these tests, placentas passed through a meat chopper were placed in cheesecloth bags and all the fluid was drained off insofar as possible. This first fraction was called placental serum although it undoubtedly contained some extracellular tissue fluids. The material was then extracted several times with salt solution and centrifugated in a basket centrifuge. After these extractions the material remaining was again extracted several times with salt solution rendered slightly alkaline. In figure 1 is shown the proteins

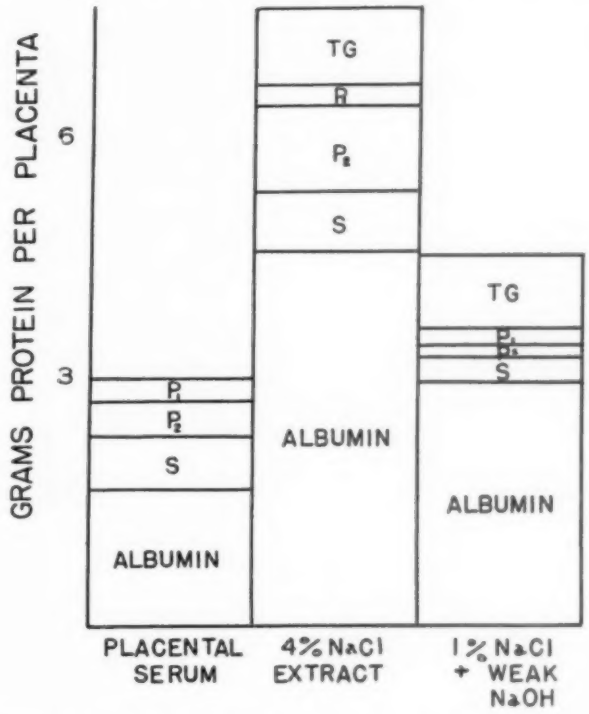

FIG. 1. Amounts and types of proteins obtained in successive extractions of placentas.

obtained by these three successive types of extraction. It is to be noted that the amounts of protein obtained were considerably greater when the organ was extracted with salt solution or alkalinized salt solution than when the serum was allowed to drain out of the ground tissue.

In the separation of the various proteins from the successive extractions, a combination of the salting out processes and of isoelectric precipitations was finally adopted as more satisfactory than either method of separation alone. Nevertheless, the separation of the individual fractions was not complete inasmuch as some overlapping of fractions occurred. Fraction S represented largely pseudoglobulin, while fractions P_1, P_2 and TG repre-

sented euglobulins, the last probably derived from the placental tissues inasmuch as it was present in negligible amounts in placental blood serum. For immunologic tests, the same protein fractions from the separate extractions were usually pooled.

Determinations of the association of different antibodies with the various globulin fractions showed that the diphtheria and scarlet fever antibodies were present only in the more soluble globulins (fractions S and P_2) while the measles and poliomyelitis antibodies were present in all fractions—poliomyelitis certainly and measles probably—even in the large molecule globulins derived from tissue proteins, TG. This was thought to indicate an association of the immune substances active against the virus diseases, poliomyelitis and measles, with tissue proteins, as well as with blood proteins, in contrast to scarlet fever and diphtheria antitoxins which were not demonstrable in some of the tissue proteins.[3]

Use of Placental Extracts in Prevention and Modification of Measles

The most extensive clinical trial of the globulin extracts has been in the prevention and modification of measles. For this purpose more than 1300 children have received injections of the extract. The results are shown in table 1. The material used in these studies represented the above mentioned fractions alone as well as in further subdivisions or in combinations. The derivation of the fractions is indicated in the table.

Table I

Placental Extract for Prevention or Modification of Measles; Intramuscular Injection

Solution or Fraction		Cases	Protection		Modification		Failure	
T	(0–50)	214	170	79.5%	39	18.2%	5	2.3%
M	(28–50)	415	294	70.8%	95	22.9%	26	6.3%
R	(28–50)S	99	82	82.8%	12	12.1%	5	5.1%
S	(0–50)	201	135	67.1%	60	29.9%	6	3.0%
P	Iso. P.	100	59	59.0%	31	31.0%	10	10.0%
FP		37	22	59.3%	14	38.0%	1	2.7%
V	(S–TG)	22	12	54.5%	10	45.5%	0	0
W	(T–TG)	6	4	66.6%	2	33.3%	0	0
Total		1094	778	71.1%	263	24.1%	53	4.8%
Commercial Extract		247	181	73.3%	58	23.4%	8	3.2%
Total Cases		1341						

Collected statistics of the use of adult immune serum and of convalescent serum in comparison with the results obtained by the use of placental extract are shown in table 2.[4] Obviously criticism of these results can be made because they represent all types of exposure and doubtless include many cases which were not actually infected with the disease. We have taken cog-

nizance of this fact and have subjected the results obtained in the use of placental extract to a more rigid test by excluding cases exposed in institutions or at play, unless the development of measles indicated that they

TABLE II

Patients Treated for Prevention or Modification of Measles with Adult Serum, Convalescent Serum and Placental Extract

Procedure	Number of Cases	Protected		Modified		Failed	
Adult Serum	584	329	56.4%	139	23.8%	116	19.8%
Convalescent Serum	1627	1227	75.4%	273	16.8%	127	7.8%
Placental Extract	1341	959	71.5%	321	23.9%	61	4.6%

Figures for adult serum and convalescent serum collected from the literature.

had actually been infected. This procedure served to increase the number of failures and modifications in comparison with the number of cases completely protected. However, it represented the most stringent test of the material. Under these circumstances, among 174 children given the material in order to protect them from the disease, 60.9 per cent were protected, 32.2 per cent had the disease in a modified form, and in 6.9 per cent the extract was without effect. Among 457 children, similarly intimately exposed, who were given the extract later in the incubation period in order to secure modification of the disease, 45.5 per cent were completely protected, 46.8 per cent had the disease in a modified form and 7.7 per cent showed no amelioration in the severity of the illness. As regards dosage it would seem that placental extract is equal to or superior to fresh convalescent serum, inasmuch as the effective dosage has varied from two to six c.c. depending on the nitrogen content of the lot, whereas the dosage of convalescent serum is usually stated to be from four to eight c.c. and that of adult immune serum to be 15 to 20 c.c.

It was thought early in the investigations that the necessary dosage of various lots of extract might be determined by measuring the diphtheria antitoxin content. However, the anticipated parallelism between diphtheria antitoxin and the measles antibody was not found inasmuch as the distribution of the two antibodies was different. It was found to be possible to have a preparation effective against measles which contained no diphtheria antitoxin. Although at best it is a rough guide, the nitrogen content has remained the most reliable index of measles antibody content.

A study of the other factors influencing the effectiveness of placental extract in measles prophylaxis has been presented in some detail elsewhere.[5, 3] Suffice it here to say that the material given by intramuscular injection in proper dosage is effective in the prevention and modification of measles, and that placental extract can be prepared on a large scale, eliminating one of the obstacles which has hindered the wider use of serum in

measles prophylaxis. In common with other types of passive immunization, the protection is of only a few weeks' duration, unless the disease occurs in modified form, in which case permanent immunity is generally believed to result. However, accurate observations on the degree of modification that will still permit the development of permanent immunity have not been extensively made. The studies of Debré indicate that the patient must have, although in mild form, definite symptoms of the disease.[6]

Reactions

The intramuscular or subcutaneous injection of placental extract has been accompanied occasionally by moderately severe reactions. The character of the reactions has seldom been that of specific sensitization. Among the 1300 patients who have received the extract there were three cases of urticaria coming on within an hour and subsiding in 24 hours, apparently accelerated reactions of allergic type. Two of these occurred in children with long allergic histories. No cases of typical serum disease have followed the use of the extract, nor have instances of sensitization to subsequent injection of the extract been encountered, although numerous children have received several injections at intervals of weeks or months. Reactions have consisted of local inflammation accompanied at times by fever. Suppuration has not occurred, nor has a local reaction lasted longer than three to four days. Febrile reactions characterized by temperatures as high as 103° F. have lasted as long as 24 hours. Among 1232 cases, mild local reactions occurred in 312, or 25.3 per cent, while more severe local reactions occurred in 49, or 4 per cent. Febrile reactions occurred in 182, or 14.8 per cent. Of these, 31, or 2.5 per cent, had temperatures above 101°. The tissue protein may be in part responsible for reactions, inasmuch as injections of the tissue protein fractions, although prepared to contain less than half the nitrogen of the pseudoglobulin fractions have been followed by twice as many reactions.

Several investigators have pointed out the marked toxicity of the press juice and of the saline extracts obtained from human placental tissue.[7] It was noted that the toxicity of such extracts was lost gradually, particularly if the extract remained in contact with normal serum. Placental extracts prepared for immunologic use have likewise shown fewer reactions after aging than when used immediately after preparation. In the lots recently prepared most of the tissue protein has been removed. Reactions have been greatly reduced in frequency and severity but have not been entirely eliminated, indicating that tissue proteins are responsible for only a part of the difficulty. Sex hormones are present in the extract in negligible amounts, apparently being almost completely removed in the process of preparation.

Immunizing Effect Following Oral Administration

Because of the short duration of immunity following the injection of the extract and the desirability of avoiding the unpleasantness of repeated injection, consideration has been given to trial of other methods of administration. Bovine lung tissue protein and human placental tissue extracts have been shown to be active in shortening the coagulation time of the blood following oral administration despite the susceptibility of these extracts to destruction by acids and alkalies and by intestinal ferments.[8, 9] The further consideration that the tissue protein (TG) was the largest protein aggregate which we have separated from the crude extract of the placenta, suggested that the antibodies might also be active following oral administration.

Studies of passive transfer tests and other allergic phenomena in both young and mature persons leave no doubt that at least minute amounts of protein may be absorbed from the gastrointestinal tract in antigenically active state by individuals of any age, without the intestines having been flooded with the protein and without the institution of measures to suppress intestinal functions.[10] Although the passage of minute amounts of unchanged proteins through the intestinal wall must be considered to occur with regularity, the passage of an antiserum in active form in sufficiently large amounts to render patients immune to disease cannot be deemed to be established.

Even if the proteins were absorbed unchanged, the duration of their presence in biologically active form in the blood stream following oral administration must be considered. In general, foreign proteins are thought to leave the blood stream within a few hours and to disappear from the urine in 24 hours. Obviously such a result would be unsatisfactory following administration of an antiserum.

The immunizing effect of placental extract by oral administration has been studied by observing the effect of ingestion of the extract on the Dick test of patients susceptible to scarlet fever, and the effect of the extract in the prevention and modification of measles in non-immune children intimately exposed to the disease. Before determinations of the immunizing effect were made, placental extract was ingested by members of the laboratory staff to be sure that the material did not cause digestive disturbances and that it was not unpleasant to take.

The immunizing effect of placental extract following oral administration could most readily be followed by testing for absorption of the scarlet fever antibody inasmuch as placental extract by intramuscular injection had already been demonstrated to render susceptible patients negative to the Dick test.[11, 3] Furthermore, not only could the reversal of the Dick reaction be readily determined, but the duration of such a reversal could be followed. In the series of tests placental extract in total amounts ranging from 9 to 20 c.c. varying somewhat with size and age of the child, was ad-

ministered in several doses of two to five c.c. each in ice-cold water on an empty stomach at least one hour before meals, according to the technic described by Mills for the absorption of the blood coagulant derived from lung tissue.[8] A Dick test performed 48 hours before the beginning of the administration of serum had been strongly positive in each person subjected to the test. The results of the test are shown in figure 2.

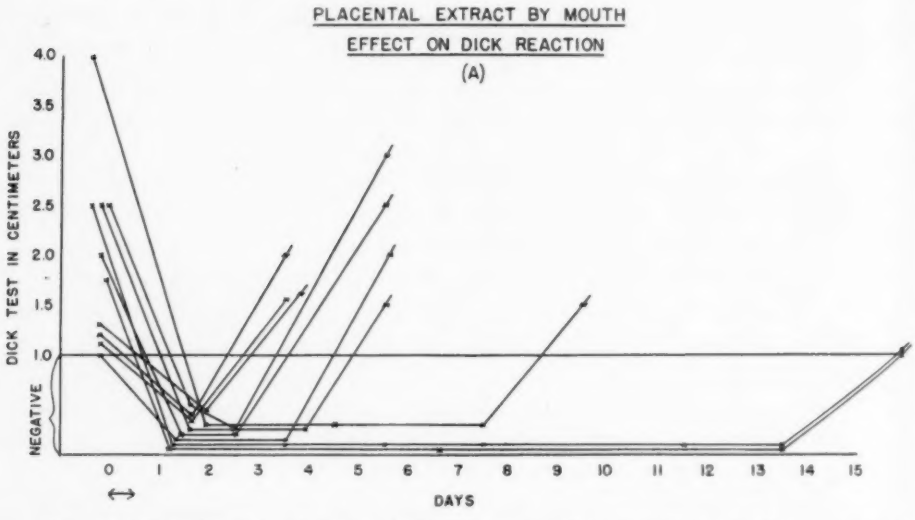

FIG. 2. Placental extract given in three doses within a period of 12 hours, in ice water, on an empty stomach. The following morning Dick tests which were previously positive were entirely negative. The negative state, however, persisted for a comparatively short time.

It is to be noted that in these observations on children, in no instance was there a failure of the effect of the material, as in each instance a reversal of the Dick reaction was obtained. The duration of the effect, however, was quite variable. Presumably the short duration in several cases was due to the absorption of only a small part of the extract administered.

Various dosages and methods of administration have been employed in an effort to secure a more prolonged effect. One method has been the administration of the extract in an iced alkaline carbonated water. In figure 3 it will be seen that with this vehicle a prompt reversal of the Dick test was obtained in seven children who received the extract in this manner. Unfortunately not all of these patients could be followed until the Dick test had again become positive. However, in each patient the test remained negative seven days or longer. In one patient who could be followed the Dick test remained negative till the eighteenth day after administration of the extract.

In all, 22 children, ranging in age from 18 months to 10 years, have been studied and in each case a reversal of the Dick test has been obtained. Adults have required larger doses of extract than children and have devel-

oped a negative Dick test only after several days and in some instances not at all.

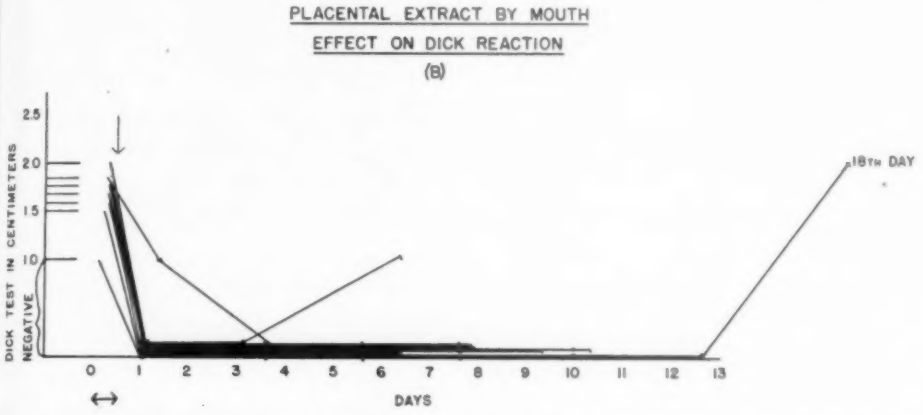

FIG. 3. Placental extract given in three doses in iced alkaline carbonated water on an empty stomach. The following day Dick tests previously positive were negative and remained negative for a considerable period of time.

The effectiveness of placental extract by oral administration in the prevention and modification of measles has been tested in over 100 patients. Eighty-four of these patients were non-immune children intimately exposed in their homes to other members of the family suffering from the disease. The results in these 84 patients, where exposure was definitely known, are shown in table 3.

TABLE III

Prevention and Modification of Measles by Oral Administration of Placental Extract

		Protection	Modification	Failure
Given to Prevent	18	7	5	6
Given to Modify	66	15	32	19

If prevention was desired, the extract was given early in the incubation period. If modification was desired, the extract was given later in the incubation period of the disease. Although the group of patients in whom the extract was tested is not large enough to permit a statistical analysis of the results, there can be no doubt that placental extract by mouth has some effect in the prophylaxis of measles. However, the results are much less striking than those obtained by intramuscular injection of the material. The dosages used by mouth have been from two to three times those used for intramuscular injection. Further attempts to secure dependable results by the oral administration of the extract would appear justified.

No reaction has been observed in any patient who received placental extract by mouth although dosages up to 40 c.c. in 24 hours have been given. Material which caused moderately severe reactions when injected intramuscularly has been given by mouth without any untoward effect.

SUMMARY

Protein extracts composed of the globulins derived from the human placenta contain diphtheria and scarlet fever antitoxins, and antibodies which neutralize poliomyelitis virus and protect exposed, susceptible children against measles.

The extracts can be prepared on a large scale and have been found useful in the prevention and modification of measles. Over 1300 children have received injections of the material. A small percentage of patients who have received injections of the extracts have had moderately severe local or general reactions.

Tests of the immunizing effect following oral administration of placental extract have been made.

Twenty-two children with positive Dick tests have been rendered Dick negative by the oral administration of the extract in cold water on an empty stomach. The duration of the negative stage has been variable but has been prolonged to as much as 18 days, if iced alkaline carbonated water was used as the vehicle. The reversal of the Dick test could not be obtained with any regularity in adults.

Tests of placental extract by oral administration in the prevention or modification of measles suggest that placental extract by mouth may be effective in this disease. Oral administration of the extract has not been accompanied by reactions.

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FEVER THERAPY IN GONORRHEAL ARTHRITIS AND CHOREA *

By Truman G. Schnabel, M.D., F.A.C.P., and Ferdinand Fetter, M.D., *Philadelphia, Pennsylvania*

Gonorrheal Arthritis

For the past forty years there have been occasional reports of cure of gonorrheal infections during a febrile illness. In 1893 Bogdan and Barthelemy [1] told of a gonorrheal discharge which disappeared during an attack of pneumonia and recurred after the fever subsided. They also noted two cases in which the development of typhoid fever caused a gonorrheal discharge to disappear. Culver [2] noted the cure of a urethral infection of Neisserian origin after four days of malaria. However, it was not until the work of Carpenter, Boak, Mucci and Warren,[3] who determined the thermal death time of the gonococcus, that the use of fever in treating this type of infection was put on a scientific basis. These investigators, working with 15 strains of the organism, found that 99 per cent of them were destroyed at a temperature of 41° C. (105.8° F.) in four to five hours. From 11 to 23 hours longer at this temperature were required to kill the remaining 1 per cent. At a slightly higher temperature, between 41.5° C. (106.7° F.) and 42° C. (107.6° F.), 99 per cent of the gonococci were killed in two hours while the remaining 1 per cent required five to twenty hours longer. These workers thus showed conclusively that the gonococcus could be killed by a temperature which the human body could tolerate. It remained only to perfect a safe and accurate method for inducing temperature of this height.

Fever produced by various methods has been used clinically in treating arthritis of gonococcal origin since 1917, and in all reported cases with better results than with any other form of treatment. Culver [2] used intravenous injections of killed gonococci, meningococci, or colon bacilli to produce the fever and reported marked improvement in 22 of 24 patients so treated. He did not, however, attribute this improvement to the fever per se. Dumitresco and Petrea,[4] using antichancroidal vaccine to elevate the temperature, reported excellent results in five cases of gonorrheal arthritis. More recently, various physical methods of inducing fever, which are more accurate and can be better controlled, have been used. Bishop, Horton and Warren,[5] using high frequency currents to produce the fever, stated that of all the arthritic patients treated by them, those with gonorrheal arthritis were the most improved. Atsatt and Patterson,[6] employing electropyrexia,

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From the Department of Fever Therapy, Philadelphia General Hospital, Philadelphia, Pennsylvania.

reported recovery in 7 out of 8 cases of acute gonococcal arthritis. Desjardins, Stuhler and Popp,[7] using the Kettering hypertherm, which I shall describe presently, have reported good results with fever therapy in 29 cases of gonorrhea, in 10 of which gonorrheal arthritis was a complicating factor.

The Kettering hypertherm, which we have used also, has been developed by Dr. Walter M. Simpson of the Miami Valley Hospital at Dayton, Ohio, Mr. C. F. Kettering, Director of Division of Research of General Motors Corporation, and Mr. Edwin C. Sittler, engineer in the same organization. In this apparatus the patient lies free in an air conditioned cabinet, surrounded by a moving current of heated and humidified air, by means of which the temperature is raised. No electrodes are in contact with the patient and no high frequency currents used. The patient's temperature and pulse are taken every 15 minutes or oftener. The temperature reaches the desired level in from 60 to 90 minutes. More detailed descriptions of this method and technic have already been given.[7, 8, 9]

The contraindications to fever therapy must be heeded, such as advanced age, renal and cardiac disease (particularly the hypertensive and arteriosclerotic types) and, in general, pulmonary tuberculosis. It must likewise be emphasized that treatments should be given only by trained nurse technicians, one to a patient, who keep continual watch over the patient, and that the work must be under the constant supervision of a physician who has been especially trained in fever therapy. It must be remembered that any fever treatment is a serious and a difficult procedure and that a patient should never be subjected to it without thorough preliminary study.

Cases of Gonorrheal Arthritis Treated. The technic of the treatment of these patients is as follows: the temperature is raised to 106° F. (rectal) and maintained between this level and 107° F. (rectal) for 5 hours. This constitutes one treatment. The treatments are given at weekly intervals; the number required varies, but is usually from two to five.

At the Philadelphia General Hospital, we have treated 18 patients with gonorrheal arthritis by fever induced in the Kettering hypertherm. In nine of these cases, the arthritic process was acute (of less than six weeks' duration); in nine it was chronic (of more than six weeks' duration). Diagnosis of the gonorrheal etiology of the arthritis was made on the basis of a history of a purulent urethral or vaginal discharge which had been diagnosed gonorrheal in origin, the finding of the gonococcus in urethral, prostatic, or cervical smears, or the presence of a positive gonococcal complement fixation reaction in the blood, or a combination of these findings.

Acute Gonorrheal Arthritis. In this group of nine patients, the average duration of the arthritic symptoms before treatment was three and one-half weeks. The earliest case treated was of two weeks' duration; the oldest case was of five weeks' duration. The number of treatments given each patient varied from two to six; the average number of hours of treatment over 106° F. was 14.5 hours per patient, corresponding to an average of

three treatments per patient. In two of these patients the gonococcal complement fixation reaction in the blood was positive before treatment. One of these reactions became negative after completion of the series. One remained positive although this was in one of the patients clinically cured. Positive urethral or cervical smears, when present, became negative after treatment, and any discharge, if present, likewise stopped. The improvement in the involved joints was striking in all cases, and in some almost miraculous. Invariably there was marked diminution in swelling and redness of the involved joint after the first treatment, and marked decrease in pain associated with definite increase in movement. The improvement was most rapid in the most recently involved joints. The temperature of the patient was invariably lower after the first treatment than it had been before. One patient who had had continuous fever going as high as 102.5° F. before treatment had no elevation of temperature after the first fever session.

Six of the nine patients were cured by the fever treatments, with no other form of therapy. Two of the remaining three showed about 80 per cent improvement after fever therapy alone, but needed baking and massage of the affected joint to get complete return of movement. In only one case was the result relatively poor. This patient still has a partial ankylosis of the left elbow, although she is able to perform practically all necessary movements with this arm and there is no active infection left in the joint. We felt that her end-result was not as good as it should have been only because she did not receive enough treatments. Because of extreme lack of cooperation on her part and a pecular difficulty in raising her temperature we were able to give her a total of only nine hours and 50 minutes over 106° F.

These results are summarized in table 1.

Chronic Gonorrheal Arthritis. In this group of nine patients the average duration of the arthritic symptoms before treatment was seven and one-half months. The earliest case treated was of three months' duration, the oldest of 18 months'. The number of treatments varied from one to six. One of the patients received only one treatment because he did not return for subsequent sessions as he had been instructed to do. However the reason for this, as we learned on follow-up examination, was that he had been entirely symptom-free after the first treatment. The average number of hours of fever over 106° F. was 18 per patient, corresponding to an average of approximately three and one-half treatments per patient. Three of the nine patients had positive gonococcal complement fixation reactions in the blood before treatment was started. All of these reactions became negative after the treatments were completed. Positive cervical and prostatic smears, when present, also became negative, and any chronic discharge, if present, stopped. The joint symptoms of all of these patients improved, although usually not as rapidly as they did in the acute cases.

Of the nine patients five were cured and have remained so since completing their treatments (for periods of from three to six months), except that one of these patients developed a fresh case of gonorrhea and con-

sequent new joint pains for which we can feel no responsibility. Three of the nine patients showed marked improvement. They obtained complete eradication of the infected process in the involved joints with relief from pain, and had a partial return of movement. Two of these three patients had previously been bed-ridden with continuous fevers for periods of three and one-half and three months respectively before treatment. After completing the fever sessions, and with local physiotherapy (baking and massage) they have been able to return to doing light housework. Only one of the nine patients has shown merely moderate improvement after treatment. He has marked increase in movements of the involved joints, but still has occasional pains.

These results are summarized below.

TABLE I

Cases of Gonorrheal Arthritis Treated with Fever Therapy

	Number of Patients	Average Duration of Symptoms before Treatment	Average Number Hours Treatment over 106 F.	Results		
				Cure	Marked Improvement	Moderate Improvement
Acute	9	3½ weeks	14½ hours	6	2	1
Chronic	9	7½ months	18 hours	5	3	1

CHOREA

Fever therapy for its own sake was first used in the treatment of Sydenham's chorea by Mas de Ayala [10] in 1930. This investigator used the *Treponema hispanicum* to produce relapsing fever in a boy with chorea of two years' duration. After four febrile attacks improvement began and continued until the boy was cured. Prior to this work improvement in patients with chorea had been noted by von Kern [11] as a result of intramuscular injections of milk, but the improvement was not attributed to the resulting fever. Horton [12] likewise observed improvement in two patients with chorea after intravenous injections of a pure protein prepared from ox-blood fibrin. He did not mention whether there was a febrile reaction, but undoubtedly there was. In 1928 Small [13] reported improvement in 24 of 25 patients with chorea treated with his *Streptococcus cardioarthritidis* antiserum. However, he considered that the improvement was due to the specific serum and not to a non-specific protein reaction with associated fever. In 1913 Pilcher and Gerstenberger [14] noted that the patients with chorea who were improved after treatment with phenyl-ethyl-hydantoin (nirvanol) were those who reacted to the drug by developing a rash and a fever, while those not so reacting were not benefited.

Sutton [15] was the first to use fever therapy in a large number of patients with chorea. This worker had noted improvement in a patient who had re-

ceived phenobarbital to the point of toxicity and who had developed a rash and a fever. Believing that the fever was the beneficial agent in this case, and in the reported cases of improvement with phenyl-ethyl-hydantoin, she decided to try typhoid-paratyphoid vaccine intravenously to produce fever. Her results, reported in this and in a later paper,[16] were very gratifying. In the latter she compared the results of 150 cases of chorea treated without fever prior to 1930 with 150 cases treated with fever after 1930. There was a striking reduction in the duration of the disease in all fever treated cases compared with those not so treated.

Many reports of the use of typhoid-paratyphoid vaccine to produce fever in patients with chorea have appeared since Sutton's work. All investigators have found that the course of the disease is noticeably shortened by this method of treatment. Another type of fever producing agent used in treating chorea was "Soufrogel" a sulphur gelatine preparation used by de Castro-Freire [17] intramuscularly. The resulting elevation of temperature to 38.5° to 40° C. was effective in reducing the duration of the disease in 11 cases so treated.

In view of these facts it was logical that physical means of inducing fever should be tried in treating these patients. While no more effective than fever induced by typhoid-paratyphoid vaccine, this method is, we feel, more accurate and the fever more easily controlled.

In our first cases we used temperatures of 103° to 104° F. for three hours and repeated the treatments at weekly intervals. Subsequently we found that the patients improved more rapidly after temperatures of 105° to 106° F. and with treatments given twice a week. Our present technic is, therefore, to give three hour sessions at 105° to 106° F. twice weekly. As many treatments as are needed are given; usually from three to five suffice. In our experience the presence of a coexisting rheumatic cardiac lesion has not been a contraindication to the treatment. Several of our patients had rheumatic mitral valve lesions and behaved as well under treatment as did those whose hearts were apparently normal.

Cases of Chorea Treated. We have completed treatments on 11 children affected with Sydenham's chorea. Of these, three had severe choreiform movements (one was so active as to require constant restraint), six had moderately severe chorea, and in the remaining two the condition was relatively mild. The age of the patients varied from 4 to 15 years. The duration of the disease before treatment was given varied from three and one-half weeks to two years (this last was one of the mild cases). In seven of the eleven patients, however, the duration of the symptoms was less than six weeks. The average number of treatments given was four, each treatment consisting of three hours of elevated temperature. In six of the eleven children there was an associated mitral valvulitis. The other five had no evidence of heart disease.

In most cases there was a striking diminution of the choreiform movements after the first treatment. In general the degree of improvement was

proportional to the severity of the process, those with the most marked movements showing the most rapid improvement. We also observed that the children with generalized movements improved more rapidly than did those in whom the movements were localized. Of the 11 cases, nine were cured after their treatments and so far (from one to six and one-half months afterwards) have not shown any recurrence. The other two did not show complete cessation of their symptoms. One child still has slight incoordination of the right hand in performing voluntary movements, but he is able to be back at school and to keep up with his class. The other child has continued to have slight movements of both arms when excited. It seems significant that both of these children were among our earlier subjects on whom we used the lower temperatures. We believe that higher temperatures would have cured them, but they were so much improved by the lower temperatures that further treatment seemed a counsel of perfection.

In all cases, the rapid improvement after the first or second treatment, with no other form of therapy, showed clearly that the fever was the effective therapeutic agent. The older children even realized this themselves, and after the first one or two treatments were anxious for more in spite of the discomfort attendant upon these sessions. In those cases in which there had been previous attacks of chorea the family physician or the parents said the improvement was much more rapid with fever therapy than without.

These results are summarized in the following tabulation.

TABLE II

Cases of Chorea Treated with Fever Therapy

Number of Cases	Age Range	Duration of Symptoms before Treatment	Average Number of Treatments	Resuts	
				Cure	Marked Improvement
11	4–15	3½ wks. to 2 yrs. (in 7 cases less than 6 weeks)	4	9	2

One case of chorea treated by us has not been included in the series above because of a fatality following the first partial fever session. This was a boy of 12 years with moderately severe chorea of three weeks' duration, and with no history of any previous rheumatic infection (rheumatism, sore throats or previous attack of chorea). His heart was normal on physical examination and his electrocardiogram was normal. After being in the cabinet for only one and one-half hours, he suddenly went into collapse with a fall of blood pressure to zero, marked cyanosis, and a cardiac rate of over 180. He was immediately removed from the cabinet and given treatment for shock. His temperature rose to 108° F. (rectal), but it responded to sponges and other fever reducing measures. His condition improved gradually but steadily for nine hours after being removed from the cabinet. His

temperature dropped to 101° F. (rectal), his cyanosis diminished markedly and he was entirely conscious and responded normally. His cardiac rate remained at 160 but was regular. His clinical condition at this time seemed quite satisfactory. Subsequently, however, his temperature and cardiac rate rose again and the cyanosis returned. This time efforts at stimulation and reduction of the temperature were without effect. He died 17 hours after his initial collapse.

At autopsy the chief gross changes were in the brain. These consisted of intense edema and venous congestion. Grossly, the heart was entirely normal. The adrenals showed mild parenchymal degeneration and the thymus slight hyperplasia. There was acute passive congestion of the lungs, spleen, liver, kidneys and the gastrointestinal tract. Thus it seems apparent that death was due to a cerebral disturbance and particularly a disturbance in the heat regulating mechanism.

It is clear that this death was a direct result of the fever treatment, but it should be stressed that this boy was treated under exactly the same conditions as the many patients we have successfully treated and that he seemed in every way an excellent subject. Such a death is perhaps comparable to the unforeseen deaths under anesthesia and should be viewed in the same light. Only time and a compilation of facts will tell whether such accidents are to be so frequent as to counterbalance the favorable results of fever therapy or whether, as in the case of anesthesia, they will be but an unfortunate but relatively small item in a desirable and beneficial whole. We hope and believe the latter will be the case.

Summary and Conclusions

Fever induced by circulating humidified hot air in the Kettering hypertherm was used in treating 18 cases of gonorrheal arthritis, nine acute and nine chronic, and 12 cases of Sydenham's chorea.

Of the nine patients with acute gonorrheal arthritis, six were cured, two were markedly improved, and one was moderately improved. Of the nine with chronic gonorrheal arthritis five were cured, three markedly improved, and one moderately improved.

Of the 12 patients with chorea, nine were cured and two markedly improved. One died as a result of a disturbance of his heat regulating mechanism.

With the exception of this unpredictable accident, no case of either of these diseases has failed to respond favorably to this form of treatment. We believe that fever therapy offers the best chance of cure for both gonorrheal arthritis and chorea.

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DERMATOMYOSITIS; REPORT OF A CASE WITH A REVIEW OF THE LITERATURE *

By Israel H. Marcus, M.D. and Joseph Weinstein, M.D.,

Brooklyn, New York

Dermatomyositis is a disease still frequently unrecognized. Because of this and the relative rarity of the condition, as well as the profound and extensive changes found postmortem in our patient, we have deemed the following case and a review of the literature as worthy of publication.

Case Report

J. K. was admitted to the Jewish Hospital on May 18, 1931, complaining of generalized weakness and difficulty in swallowing and speaking. He was of the Hebrew race, born in the United States, 44 years of age, and a paper cutter by trade.

Family History. Negative except for the fact that two of his maternal uncles and three of his sisters had all died of carcinoma of the stomach.

Past History. The patient had had scarlet fever in childhood without any complications; pneumonia at 17; influenzal bronchopneumonia at 31; bilateral keratitis, according to his belief, since birth, but inactive for the last 15 years; and frequent sore throats for many years. Two months before admission (i.e., one month after the onset of the present illness) he suffered a generalized urticarial rash following the administration of tetanus antitoxin for an injury to a finger.

He had always worked hard. He used alcohol, tobacco, tea and coffee in moderation. He had been married 22 years and had seven healthy children. His wife had one miscarriage—in her fourth pregnancy.

Present Illness. Three months before admission to the hospital the patient noticed soreness and weakness in both arms and forearms, occurring with activity. Associated with this there was a gradually increasing limitation of motion of the elbows and shoulders. Two months after the onset, the soreness and weakness were felt in the lower extremities, involving later the muscles of the lower back and pelvis also.

Two months before admission he first experienced an inconstant, but progressive, dysphagia; at first noted only with the taking of solids but later with liquids as well. The food seemed to him to get stuck in the suprasternal region, and there was frequent regurgitation through the nose.

For the last six or eight weeks he had been hoarse, and for the last 10 days there had been a rapid fatiguing of the organs of speech, affecting markedly his pronunciation.

He had had a slight cough for about six weeks, and in the last two weeks a slight dyspnea.

Three days previously he had first noticed a swelling of his face and arms. He had never observed any muscular twitchings or atrophies. There was no history of double vision. There was no apparent loss of weight.

Physical Examination on Admission. The temperature was 100.2° F.; pulse 90, respirations 18, per minute.

The patient was a hyposensitive individual, appearing comfortable, fairly well nourished, coöperative and intelligent. His hair was gray, with scattered areas of

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alopecia of the scalp. There was an erythema and dry scaliness of the scalp, nose, nasolabial folds, and ears. The lower eyelids were edematous, and there was a puffiness and irregular erythema of the cheeks. The face had a peculiar mask-like appearance; but a display of emotion could be elicited. The pupils were equal in size, slightly irregular, and reacted well to light and accommodation. The fundi were normal. There was a keratitis of both eyes, with pannus formation and scarring of the conjunctiva of the lids. The ophthalmologist considered the condition an old trachoma with corneal involvement. The few remaining teeth were carious. There was a postnasal drip. The uvula drooped abnormally, but the pharyngeal reflex was present. The thyroid was palpable, but not enlarged. There was a generalized acne of the chest anteriorly and posteriorly. Lung examination revealed harsh breathing at the right apex, an occasional moist râle at the right base posteriorly, and a suppression of the breath sounds and fine crepitant râles at the left base posteriorly. The heart was normal in size, and regular in rate. There was a roughening of the first sound at the apex with a suggestion of a presystolic murmur. The second pulmonic sound was accentuated. Blood pressure was usually about 125 mm. Hg systolic and 75 mm. diastolic. There was no abdominal tenderness or spasticity, and no viscera or masses were palpable. The rectal sphincter was somewhat relaxed. The prostate and genitalia were normal.

There was a slight swelling of the upper part of the arms, more marked on the right, and a diminution in the muscular power of the upper extremities, more marked on the left side. There was a flexion deformity, with inability to flex both elbows beyond 15 or 20 degrees. Forced flexion caused considerable pain. There was muscle tenderness on deep palpation. The muscles of the lower extremities appeared smaller than normal. The knees could not be flexed beyond about 15 degrees. There was weakness of the muscles of the pelvic girdle, and when the patient bent forward it required marked effort to return to the erect posture.

Neurological examination showed no cranial nerve involvement. The biceps and triceps reflexes were normal. The deep reflexes were present but became depressed after repeated testing. The abdominal reflexes were normal. There were no extraocular palsies. Hoffmann's sign was not present. There was a left sided equivocal Babinski and at times a bilateral Oppenheim. There was no ankle clonus. Coordination was good. There was no impairment of the cutaneous sensations. Idiomuscular contractility was marked over the upper extremities and chest. Marked dermographia was present. There was an atrophy of the thenar and hypothenar eminences and of the interossei in both hands.

Biopsy of a section of the left biceps showed on microscopic examination the following: The muscle fibers are swollen. The protoplasm assumes a fibrillar appearance, with a disappearance of the transverse striations. In some the protoplasm is homogeneous and presents a hyaline appearance. Various stages of degeneration of the muscle cells are noted, from the cloudy swelling, above described, to complete degeneration and loss of identity. There is a moderate increase in the connective tissue, which is quite dense. In the areolar tissue the large blood vessels appear normal. The arterioles, however, in many cases show rather extensive perivascular round cell infiltration. No thrombosis or occlusion of vessels is noted.

Spinal tap on May 28 showed red blood cells in the fluid, negative Wassermann and Kahn reactions, and no reduction of colloidal gold. Culture of the fluid gave no growth.

Roentgen-ray of the chest on May 20, revealed a bilateral hilum infiltration and an exaggeration of the pulmonary markings, but no evidence of localized disease. There was no radiographic evidence of a thoracic thyroid. The cardiac shadow was within normal limits of size, shape and position.

Fluoroscopic and roentgen-ray examination of the esophagus on May 26 revealed a slight delay in the passage of the opaque paste at the level of the upper end

of the sternum, which delay persisted for a few minutes, after which the opaque column passed readily through the esophagus. These findings, the roentgenologist believed, suggested the presence of spasm or localized muscular weakness.

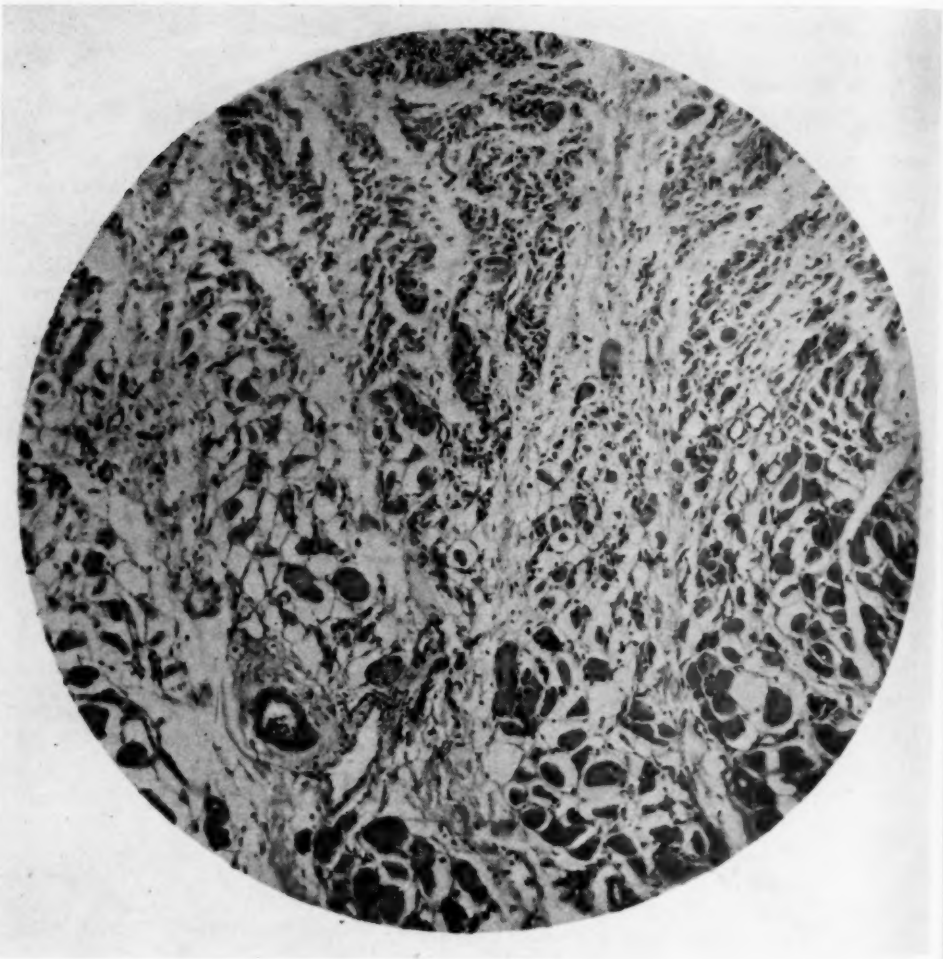

FIG. 1. Section of muscle.

Electrocardiogram on May 21 showed a ventricular rate of 107. R was slurred in all leads; the T-wave in Lead II was low, and in Lead III inverted. Q_3 was deep. These findings suggested the existence of myocardial damage.

Glucose tolerance test: Blood sugar, fasting, at 8 a.m. was 175 mg. per 100 c.c., at 9 a.m. (one hour after ingestion of 100 grams of glucose) 205 mg. per 100 c.c., at 10. a.m. 295 mg. per 100 c.c., and at 11 a.m. 206 mg. per 100 c.c. The urine at all these hours showed no sugar. These results were interpreted as evidence of a disturbed sugar metabolism, diabetic-like in nature, with a high renal threshold.

Blood chemistry tests on a fasting stomach were: Sugar 150 mg. per 100 c.c.; creatinine 1.5 mg. per 100 c.c.; urea nitrogen 15.6 mg. per 100 c.c.; and uric acid 3.7 mg. per 100 c.c.

Blood Wassermann and Kahn tests, repeated on several occasions, were constantly negative.

Urines, tested a number of times, showed a specific gravity varying between 1.018 and 1.030, were always acid, and never showed any albumin or sugar or pathological microscopic sediment.

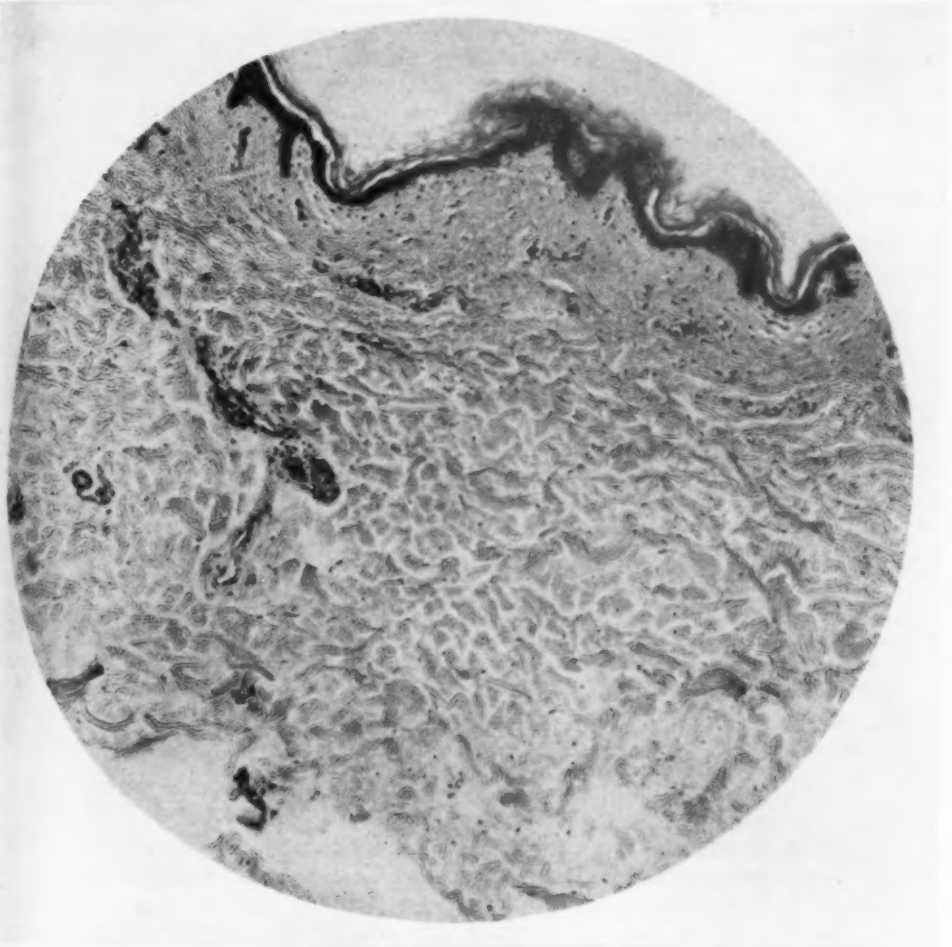

FIG. 2. Section of skin.

Blood count on admission was: Red blood cells 3,800,000 with 75 per cent hemoglobin. White blood cells 7,000 with 64 per cent polymorphonuclears (of which 8 per cent were band forms), 32 per cent lymphocytes, 4 per cent large mononuclears and transitional cells, and no eosinophiles.

Blood sedimentation time was 40 minutes for 18 mm.

Basal metabolic rate was plus 3 per cent.

Roentgen-ray of the chest on June 2 suggested an infiltration of the lungs on the left side. Sputum examination showed no tubercle bacilli, but revealed Gram negative and positive bacilli with spirilla and fusiform bacilli and micrococci catarrhalis. Culture of the sputum showed *Staphylococcus aureus*.

On June 5, three days before death, pitting edema of the lower extremities was noted, but there was no sacral edema or any edema over the rest of the trunk. The same day the patient experienced very much more difficulty in swallowing than previously.

The temperature ranged throughout between 100° and 101° with an occasional elevation to 103°. On the day before death it rose to 104°, and the respirations rose that day to 50 per minute. Moist râles were heard over the entire chest. Mucus had to be suctioned from the throat. The pulse became imperceptible and the heart sounds very weak. The patient grew worse, and died on June 8.

Treatment included the following: Pilocarpine gr. 1/20 thrice daily; ephedrine sulphate gr. 3/8 thrice daily, at first, and later increased to gr. 1 1/2 thrice daily; finally quinine urea hydrochloride gr. 7 1/2 was used intravenously each day, and calcium lactate gr. 20 thrice daily was also given. Nothing seemed to have any beneficial effect.

Autopsy Findings

The body is that of a markedly undernourished white male. The cheeks and eyeballs are sunken. The skin is dry and loose over the entire body. The subcutaneous tissue is reduced to a minimum. The muscles are extremely thin and edematous, and in areas present a gray hue.

Microscopic examination of pieces of *skin and muscle* taken from the surface of the chest and abdominal wall and from the muscle of the diaphragm and psoas muscle shows a marked atrophy of the cutis and a fibrosis of the subcutis. The fat normally present in the subcutis has completely disappeared, and the fat tissue is replaced by fibrous material. The muscle shows the following: Many of the cells have lost their cross striations, some are hyalinized, some are undergoing fibrillar changes, and many show complete disintegration of the cytoplasm. Vacuolization is present, and numerous plasma cells have infiltrated the muscle. The nuclei of the muscle cells are either thinned out and tortuous, or clumped together, or broken up. Marked edema separates individual cells. There is a perivascular round cell infiltration, which is nodular in distribution. Some of the vessels show an endothelial hyperplasia and contain fibrin thrombi and enmeshed leukocytes. Clumps of short bacilli and cocci are present in some of the muscle sections.

Macroscopically the *thyroid* appears normal, but on microscopic examination purulent thrombi are found occluding large veins, and one of these thrombosed veins shows a suppurative process in the intimal coat.

Larynx: The epiglottis is extremely edematous, as are also the aryepiglottidian folds. The vocal cords are pale, and also markedly edematous.

The mucosa of the *trachea* is congested and edematous.

The *bronchi* are congested and the smaller divisions contain a marked amount of pus and lead into patches of pulmonary consolidation.

There are some dense adhesions binding the *lungs* in places to the chest wall. The rest of the lungs is covered by a fibrinous exudate. The lungs show an extensive purulent bronchiolitis and suppurative pneumonitis.

The *peribronchial lymph nodes* are enlarged, soft, and red-blue in color.

The *myocardium* is edematous and shows on microscopic examination a moderate amount of atrophy. There are no changes in the heart muscle similar to those found in the skeletal muscles.

The *aorta* presents grossly a moderate amount of atherosclerosis.

The *liver* shows a parenchymatous hepatitis with fat infiltration.

In the upper portion of the *esophagus* are several superficial ulcerations, the bases of which microscopically show a large number of hyperplastic glands and chronic inflammatory tissue. The germinal centers of the mucosa are markedly hyperplastic. The muscle of the wall of the esophagus shows degenerative changes consisting of

granular disintegration. There is a marked edema involving all layers of the organ.

The *stomach* is normal except for a congestion of the mucosa.

The external muscular coat of the *large intestine* contains a markedly increased number of nerve ganglia, the individual cells of which ganglia show neurotrophic changes. The mucosa is ulcerated in one area, the base of the ulceration being also the site of a chronic inflammatory process. Numerous thick coccoid bacilli are seen.

The *kidneys* and *spleen* are congested and show also cloudy swelling.

There is a parenchymatous degeneration of the *pancreas* and *adrenals*.

The cells of the *bone marrow* are hyperplastic and numerous cocci are seen.

The *brain* is extremely edematous.

The *femoral nerve* is undergoing changes consisting of vacuolization of the cell cytoplasm. The process, however, is mild in character.

Historical

The earliest recorded case of dermatomyositis is one that was described by Wagner [111] in 1863 under the title of "A Rare Muscular Disease." Twelve years later, in 1875 Potain [84] recorded another case, calling it "an atypical case of chronic glanders." In 1887 the condition was carefully described by three authors independently of one another—Wagner,[112] Hepp,[41] and Unverricht.[106, 107, 108] Hepp called the disease "Pseudotrichinosis." Unverricht was the first to call it "dermatomyositis," an excellent name, for in this disease there exists an inflammation of the muscles (a polymyositis) associated with skin manifestations, such as edema and dermatitis. In 1888 Senator [93, 94, 95] described a type of polymyositis with involvement of the peripheral nerves, and called this condition "Neuromyositis." Oppenheim in 1899 [79] and 1903 [80] called attention to the fact that in this disease not only were the muscles and skin affected, but that the mucous membranes of the mouth, throat, and larynx might also be involved, and for such cases he coined the term "Dermato-mucomyositis." Oppenheim [82] in his textbook of 1923 described this disease with great thoroughness and clarity, and although in the preparation of this present article the authors have culled freely from the publications of all who have previously written on the subject, to Oppenheim beyond all others we are obligated. In view of the possible involvement, as in the case we have reported, of skin, mucous membranes, muscles and nerves, the best name given to the condition, we believe, has been "Dermato-muco-neuro-myositis." Probably in the group of cases of dermatomyositis we should include the cases collected by Lorenz [68] in 1898 under the title "Polymyositis hemorrhagica," in which there is an inflammatory sanguineous infiltration into and between the affected muscles, or in which there has been an ecchymotic discoloration of the skin. In these cases purpura and hemorrhages may occur from the mucous membranes or into the myocardium.[120]

Occurrence

Dermatomyositis occurs in both males and females, but is probably somewhat more frequent in the former.[82] Although usually occurring in

adult life, it may be seen at any age. Lehmkuhl,[62] reviewing the literature between 1895 and 1928, found 16 cases in children, the two youngest being three years old. Demel[19] reported a case of "Sclerema of the Newborn in the Form of Polymyositis." It commenced on the second day of life, and the child died when nine days old. He believes that the multiple inflammatory alterations in the infant's skin and muscles were the same as those found in adults in dermatomyositis.

Etiology

Although much has been written on the etiology of this disease, and although many interesting observations have been reported in connection with the study of the cause of the disease, at the present time we have no definite knowledge as to its etiology.

Most of the authors who have attempted to determine its causation have thought it to be due to some infectious agent. A number of facts have suggested this infectious etiology: the fact that the disease is more common in winter than in summer,[31] the existence of an enlarged spleen in the acute stage in many of the cases, the albuminuria, the rash that is so frequently present,[83] and the occurrence of a few instances in epidemics.[65, 97] In some cases bacteria have been found in the blood stream,[3, 52, 74, 78] in the muscles,[5, 37, 69, 120] and subcutaneous tissues.[30, 78] But the instances in which organisms could be thus discovered are but relatively few compared to the total number of cases that have been reported. If the disease were due to a microörganism one would expect it to be found much more often than it has been demonstrated. Various bacteria have been accused as the cause of the disease—"micrococcus polymyositicus,"[28, 73] streptococci,[24, 30, 60, 78, 118] staphylococci,[3, 5, 52, 74, 76] meningococci,[120] *Bacillus coli*, gonococcus,[22, 113, 96] Gram positive bacilli resembling the Welch bacillus,[90] and the tubercle bacillus.[37, 82] A number of cases have been observed in the puerperium,[82, 106, 107, 108, , 110, 119] and a number have been reported after influenzal angina[7, 14, 16, 75, 116] and acute articular rheumatism.[11, 21, 35, 46, 86, 114] It has even been observed after measles[50] and pertussis.[92] Not only have different men blamed different bacteria as the etiological agents of the disease, but some have even believed the condition to be due to a protozoan.[69, 99, 106, 107, 108] Is the disease only a syndrome that can be caused by any one of a number of infective agents?

A few writers have considered the disease to be due not to a microorganism but rather to a form of intoxication. Thus it has been observed in cases of food poisoning,[93, 94, 95] after exposure to cold,[36, 82] in gout,[82] in alcoholic patients,[114] and in patients with various gastrointestinal diseases resulting in ulceration of the gastrointestinal tract with possible absorption of toxic products.[2, 49, 104] Others have believed it to be due to vascular changes in the small arteries.[114] With so many conflicting opinions given, we must conclude that at the present time the disease can be attributed to no definite cause.

Pathology

The pathology of dermatomyositis will be described in great part in the following pages under the description of the disease. It need not be repeated here. It is [82] a parenchymatous and interstitial myositis, implicating the entire musculature of the body or a large part of it. A whole muscle may be involved or only a part of it.[4] Macroscopically there are edema and discoloration of the muscles, which not rarely are also the site of hemorrhages. Waxy degeneration is frequently present.[11, 58] The tissues may be so pale and the edema so great that it may be impossible to distinguish muscle from fascia.[75] Muscle, fascia, and fat—all may have the same appearance. The muscles may have a grayish yellow coloration, they may be speckled, they may be soft, or brittle or even hard. Even calcareous incrustation of necrotic muscle tissue has been observed.[40] The subcutaneous areolar and fatty tissue may also be edematous, and may likewise be the site of small hemorrhages.

Microscopically there is seen round cell infiltration of the interstitial tissue and thickened perimysium. The nuclei of the sarcolemma may be increased in number,[11] and the muscle fibers greatly swollen—to four or five times their normal diameter—with occasional large vacuoles within the muscle sheath, and numerous small hemorrhages within the intermuscular connective tissue.

Symptomatology

The disease usually begins with the general symptoms of ill health—listlessness, headache, vertigo, gastric symptoms, and a sense of heaviness in the limbs; or the patient may complain that his limbs feel as if they had grown shorter.[98] In a few instances a chill has been the initial symptom.[114] Soon drawing or tearing pains are felt in the muscles; later the patient becomes tired after walking but a few steps [72]; and finally the affected muscles gradually become completely incapable of functioning, and he lies helpless in bed, unable to move a limb, absolutely quiet—as if in a cast.[44]

Muscle Involvement

Any muscle, or any combination of muscles, may be affected. The proximal parts of the extremities are usually more involved than the distal muscles, so that the fingers are frequently unaffected at a time when the shoulders and elbows have become immobile.[82] In a few cases the disease has been limited to only one extremity, or even to an individual muscle,[81, 89] or various muscles may be affected in succession with disappearance of symptoms in one muscle as new ones are involved.[57] The cervical, dorsal, abdominal, or trunk muscles may be involved, as in our case,[88, 98] with resulting rigidity, tenderness, and pain on motion. The muscles of the jaws,[15, 16] tongue,[88] soft palate,[44, 88] pharynx, and larynx may be implicated, causing the patient to open his mouth only with difficulty, to note that his

tongue is swollen,[83] or to have disturbances of speech,[8, 23, 31, 72, 98, 114] yawning, mastication,[37] or, as in our case, even of swallowing.[4, 12, 31, 37, 44, 55, 78, 102] In a few instances the disturbance of deglutition has been the very first symptom of the disease.[55, 114] Regurgitation of food may occur through the nose. He may be unable to bring up the secretions that accumulate in his throat.[44] The diaphragm and other respiratory muscles may be affected,[11, 58, 78, 88] and asphyxia and aspiration bronchopneumonia [8] are, in fact, the most common cause of death in this disease. Rarely asthmatic attacks of short duration have been reported.[114]

In some cases the pains are first felt in the joints, and only later change to the muscles.[82]

There is swelling of the involved muscles and of the soft tissues and skin over them. The swelling frequently affects the face, especially in the region of the eyelids. The edematous, hard, tense infiltration of the skin and subcutaneous tissues may be so marked that one cannot satisfactorily palpate the underlying muscles to determine their consistency. But in some cases the skin is not swollen.[25] When the muscles can be palpated they sometimes feel hard, sometimes soft and flabby, and even a pseudofluctuation or circumscribed edema or node formation may be present.[34, 85, 98] Sometimes fluid may be aspirated from the muscular swellings.[4] The inflammatory process may extend to the tendon sheaths, and contractures are frequently seen. Rarely involuntary muscular twitchings are present.[31]

Usually the heart muscle is not affected, or at most there exists but a cloudy swelling as a result of septic disease. However, this muscle too may participate in the disease process,[31, 70, 79, 90, 120, 5] with resulting grave disturbances of cardiac function,[8] such as tachycardia independent of the existence of fever, pulse irregularities, dilatation of the right side of the heart.[78] The cardiac condition may even be the cause of death.[82, 114]

Skin

The skin of the patient with dermatomyositis is usually edematous. The edema may be of the soft or hard variety, with or without pitting on pressure.[88, 31] It invariably involves the extremities, being more marked in the proximal than in the distal parts. Any portion of the body may be involved as the lips [51, 114] or penis.[51] Or the skin of the entire person may be edematous.[102] The face, especially the eyelids, is usually the first part of the skin affected, and the process may advance here to a very marked degree [38] before any other symptom of the disease presents itself. When redness and warmth are also present, as is frequently the case, one can easily make the mistake of diagnosing erysipelas.[98]

There may be present simply an erythema of the skin or scalp,[4] or there may exist exanthemata resembling the lesions of any one of many kinds of skin diseases: roseolar lesions, maculo-papular lesions,[78] urticaria, blebs, eczema,[62] morbilliform lesions,[83] vesicular lesions [102] which may resemble

varicella [83] or lymphangioma circumscriptum, lichen planus,[75] erythema nodosum, erythema multiforme,[31] acrodermatitis,[31, 51, 98] panniculitis with nodules suggestive of erythema nodosum situated deep in the subcutaneous tissue and fat.[83] The skin may peel.[4, 72, 114] There may be localized swellings,[14, 51] which may last a long time or disappear within 24 hours, to reappear in a new area. Pruritus may or may not be present.[78, 88] The skin may take on a scar-like appearance or even look like that of a patient with scleroderma. Or it may be thickened without being edematous.[37, 114] There may be present an extreme hyperesthesia of the thickened skin.[116] If this thickening occurs in the face, especially if the facial muscles are also involved, the countenance is frequently immobile and like a mask—described by Oppenheim as "alabaster-like." The skin may be glossy, and there may exist a localized [7, 75, 98] or generalized [37] atrophy of it.

Hyperhidrosis,[57, 78] general or localized,[38] is frequently present. Hair formation may occur in unusual localities [82]; or, on the other hand, loss of hair may result.[52] Dermographia or *tache cerebrale* [9] may exist. Pigmentation of the skin may be marked.[37, 58, 114] Petechiae may be present [7, 62] or there may be blue spots on the skin suggestive of superficial hematomas in the course of absorption.[53] Areas of telangiectasia may also be present.[75]

Scleroderma-like changes have been noted in a number of instances.[2, 87] Allan's case [2] is most interesting in that, although eight months after the onset of the dermatomyositis the patient presented the appearance of marked scleroderma with loss of all motion at the elbows, when seen five years later he had almost completely recovered from his disability and the hardness and contracture of the tissues had disappeared.

Langmead,[61] Friedman,[31] and Allan [2] believed the morbid anatomy in both dermatomyositis and scleroderma to be the same. Allan observed that the essential changes in the skin and muscles in both conditions are the edema, cellular infiltration, narrowing or obliteration of the smaller blood vessels, and degeneration of the muscle fibers and skin, followed by fibrous invasion throughout and atrophy.

Mucous Membranes

Mucous membrane involvement is a frequent occurrence.[34, 48] The nature, extent, and location of the mucous membrane involvement may vary. The uvula, palate, and pharynx may be slightly reddened and glassy in appearance,[22] or vividly red and beefy.[31, 57] In Steinitz and Steinfeld's case [103] the saliva was foamy and purulent, interfering with the intake of food and with respiration. Laryngeal involvement may give rise to a weak, hoarse, high pitched voice, and to the hawking of blood tinged sputum.[38] The mucous membranes of the lips and buccal mucosa may be atrophied.[37] In Joachim's case [51] there was an eruption of "small pimples" at the edge and tip of the tongue and the inner surface of the cheeks. There may be an infiltration of the tongue, which on palpation will feel firmer than normal

(reference 103 and Barnes' case reported by Parkes Weber and Gray). The conjunctiva [78, 82] and the external auditory canal [82] may be involved. The parotids may be swollen and tender.[38] However, some observers [36] have found the mucous membranes of their cases entirely free from involvement.

Nervous System

The sensorium of the patient usually remains clear until late in the disease, when, as a result of the fever and exhaustion, there may occur mental confusion, hallucinations, and delirium.[82]

The nerves of special sense are not affected. The sensory nerves are only occasionally involved. The following are symptoms occasionally reported: hyperesthesia of the hands and fingers,[31] pains in the fingers with a sensation of numbness, [58, 114] lancinating pains in the hands and feet and tenderness at Erb's point on both sides,[67] cramp-like pains,[102] pains in the ears and in the abdomen,[67] intense pain on pressure over the femoral and ulnar nerves,[98] painful foot spasms with some degree of foot drop,[38] pain on slight touch and inability to differentiate between blunt and sharp sensations,[48] tenderness over the entire skull, especially over the supraorbital regions.[32]

The tendon reflexes are decreased or wholly absent if the corresponding muscles are involved by the disease.[82, 120] This areflexia may be due to the marked edema, to the inflammatory processes in the muscles, or to a combination of neuritis with the dermatomyositis. On the other hand, accentuation of the deep reflexes has been reported.[67] A positive Babinski sign has also been observed.[62]

Because of the resistance which edema offers to the electric current [62] it is very difficult, and at times even impossible, to make electrical examinations.[82] The result is a quantitative decrease or even a complete loss of excitability (particularly to the direct current). Frequently it is impossible to test for electric excitability because of the patient's severe pains.[62] In mild forms of the disease, however, the reaction to electrical excitability may be entirely normal.[82]

The skin reflexes may be normal.[82] A pseudo-Kernig's sign [78] has been reported, due probably to infiltration of the extensor muscles of the thighs. Signs similar to those observed in syringomyelia have also been observed.[26] Vasomotor symptoms may be present, such as a red or bluish discoloration of a limb, which may be cooler than that on the opposite side.[67]

In the extremely rare condition known as neuromyositis the neuritic symptoms are prominent, whereas the other manifestations of dermatomyositis, such as marked swelling of the muscles, edema, and exanthema of the skin, are absent. Although the nerve trunks are painful, the involved muscles are not sensitive to touch. There are disturbances of electrical irritability and also sensory disturbances. The reflexes are affected, and vasomotor disturbances are nearly always present. Later on in the disease

atrophic paralysis of muscles with corresponding contractures develops. Thus there may be paralytic contractures in the elbows and finger joints, the hands contracting to the fist position. Histologically in addition to the typical findings of polymyositis there is a destruction of the neurilemma and replacement of nerve fibers by connective tissue. While Steiner [100] believes that neuromyositis is practically always seen in chronic alcoholics and is accompanied by ataxia, Hoegler [46] reported a case which followed upon an attack of rheumatic pains with swelling of practically all the joints, and in which atrophy of the muscles, particularly of the arms, developed after the pain and swelling of the joints disappeared.

The eye muscles may be involved in dermatomyositis. Paralysis of the eye muscles and ptosis,[82] lateral nystagmus,[72, 111] and slight exophthalmus without Von Graefe or Stellwag signs,[44] have been observed. Oppenheim [82] reported a case in which iritis existed.

Spleen, Liver and Lymph Glands

Splenic enlargement is frequently reported in dermatomyositis.[9, 14, 31, 38, 57, 88, 103] The enlargement may be slight,[31] or the gland may be increased to even twice its normal size.[78] Van Creveld [14] noted a case in which there was a regression of the enlargement to normal size during a period of temporary improvement. Wasilieu and Eitwid [114] reported a case in which the spleen was even smaller than normal.

Some observers have found the liver also enlarged.[14, 27]

The superficial lymph glands are usually normal, but Fiedler [27] reported finding enlarged painful glands, pea-sized or smaller, in the axillary, cervical, and inguinal regions.

Other Symptoms

Arthritis is occasionally present. The involvement may be limited to a few joints [83] or generalized [55, 81] and characterized by pain, or swelling, or both.

Hemorrhages from the internal organs, especially intestinal hemorrhages, have been seen [10]; and various other gastrointestinal symptoms have been observed in children.[62]

Loss of weight may be a prominent symptom. One case lost 23 kg. (51 lbs.) in 12 days.

The temperature is usually elevated.[61] In cases running a chronic course it is not constant, whereas in the acute cases it may go even above 104° F. Schmautzer [90] was able to show new rises of temperature as new groups of muscles were affected. Cases are known, however, having completely normal temperatures throughout.

Laboratory Findings

Eosinophilia is frequently observed,[1, 16, 27, 71, 87, 116] counts as high as 76 per cent being reported.[27] The eosinophilia may persist even during periods of intermission of the disease.

The urinary findings vary, depending on the presence and degree of nephritis as a complication. The urine may show only a few red blood cells,[88] or there may be many red cells, casts, and a heavy trace of albumin.[83] The total quantity may be markedly diminished.[103] Urobilin may be present.[27] In Joachim's case,[51] although the specific gravity of the urine was 1.032 with no abnormal findings, the urea nitrogen in the blood was 27.2 mg. per cent.

An increase of the calcium in the blood to 16.8 mg. per cent was observed by Marinesco, Draganesco and Facon.[72]

Steinitz and Steinfeld found a disturbance in the creatine metabolism in their case, indicated by a permanent creatinuria and diminished elimination of total creatine, by the inability to transform orally administered creatine, and by a diminished creatine content of the muscles. They believe that this disturbance is not a primary symptom of the disease but is caused by grave anatomical changes in the muscles, and that the creatinuria is caused by diminished ability of the muscles to store creatine.

The basal metabolic rate may be normal [83, 98] or moderately elevated.[12, 51] It has been observed [12] that early in the disease, before the muscular stiffness becomes prominent, the basal metabolic rate may be elevated even though the clinical picture may resemble that of myxedema, being characterized by mental dullness, drowsiness, dry skin, harsh thin hair, thickening of the hands, pitting edema, and increased sensitiveness to cold.

Prognosis

The prognosis as to life in this disease is very grave. The prognosis is better in the cases that run a mild course early in the disease and in the circumscribed forms.[82] It is also better in childhood than in adult life.[62] However, even in severe cases recoveries have been reported.[10, 13, 21, 33, 35, 43, 45, 65, 69, 77, 106, 107, 108] Oppenheim [80] in a series of 10 severe diffuse forms of the disease observed five complete recoveries and two deaths. Steiner [101] found 17 deaths in a series of 28 collected cases. Sick [97] reported nine cases in which the diagnosis was established by biopsy of the muscles, with 100 per cent recovery. However, in these cases there was no skin involvement or edema.

The disease may continue for weeks, months, or even years. Weinberger's case [115] lasted nine years. Death may result in the early weeks of the disease, or after a few weeks complete recovery may occur. In the chronic cases remissions and exacerbations may appear.[82, 97, 110] One is not justified in considering a case as cured until after the lapse of a number of years. This is because of the possibility of the occurrence of a relapse, as in the case of van Creveld, who first reported the patient as one that had made a complete recovery,[14] and two years later reported a relapse in the same case.[15]

The usual cause of death is bronchopneumonia.[18]

Differential Diagnosis

Polymyositis, or dermatomyositis, is considered by most authorities, though not by all,[29] as a different disease from the purulent forms of muscle inflammation. Thus Oppenheim [82] well says that it is desirable to separate polymyositis from muscle abscess, just as we separate non-purulent encephalitis from brain abscess, in spite of the relation between both latter conditions.

Dermatomyositis so closely resembles trichinosis that it has been called pseudotrichinosis.[82] However, one can usually diagnose trichinosis by noting that a number of persons have been affected by the disease and that they all have eaten meat derived from the same animal. Gastrointestinal disturbances are usually present in trichinosis, but in some cases they may be absent. The muscles chiefly involved in trichinosis are the ocular, masticating and laryngeal, and they are the seat of severe pains. Edematous swelling of the face and eyelids develops at an early date in trichinosis. A positive diazo reaction favors the diagnosis of trichinosis, as does also the absence of cutaneous eruptions. As shown above, eosinophilia, which is marked in trichinosis may also be very pronounced in dermatomyositis. Moreover, eosinophilia disappears in trichinosis if mixed bacterial infection develops; it also disappears in grave cases of trichinosis shortly before death.[14] Considerable eosinophilia, furthermore, is found in grave cases of acute muscular rheumatism. Biopsy of a piece of muscle, and the finding of trichinae therein, of course establish the diagnosis.

Mild cases of dermatomyositis may be confused with muscular rheumatism, but the swelling of the muscles, the skin manifestations, the elevation of temperature, and the other phenomena of dermatomyositis, usually enable one easily to make the differentiation.

Polyneuritis may sometimes be difficult to distinguish from dermatomyositis, but the absence of muscular swelling and edema usually facilitate the diagnosis. However, as said before, cases of polymyositis with involvement of the peripheral nerves—called "neuro-myositis"—have been described.[6, 23, 93, 94] In neuro-myositis ataxia is frequent.

There is a type of dermatomyositis which is limited to one extremity, and which therefore may be confused with plexus neuritis.[117]

Localized forms of myositis, caused by excessive use or trauma of the part,[39, 82, 105] may for a time make us suspect a mild form of polymyositis. The condition may lead to a lasting induration and contraction of the muscle, but it has no influence on the general condition of the patient.

An epidemic form of myositic pseudorigidity of the neck, produced by painful swelling of some of the neck muscles, has been described.[17] However, the course of events usually easily enables us to make the diagnosis.

Syphilitic myositis also can closely simulate polymyositis.[42] However, syphilitic myositis usually does not cause such acute myositic symptoms and develops chiefly in the biceps and masseter muscles and less frequently in the pectoralis, deltoid, sternocleidomastoid, or muscles of the calves.[120]

Myositis ossificans, periarteritis nodosa,[59, 105] nephritis, erythema nodosum, erythema induratum, panniculitis, the "hypodermic type of sarcoid," and scleroderma [20, 83] may all, also, at times, simulate dermatomyositis. A complete study of such cases, however, reveals their true nature rather easily.

Diffuse exudative scleroderma, in rare cases, does not remain limited to the skin and subcutaneous tissues but involves also muscles and fascia, and causes their atrophy. Muscular atrophies in such cases are not caused by inactivity, but are the result of sclerotic processes in the muscles.[98] Moreover, in scleroderma there may be an erythematous eruption occurring concurrently with or before the characteristic changes are found; and during the course of the disease fresh eruptions may appear from time to time. During the active phase there may even be edema and fever. All these add to the difficulties of diagnosis. Several observers have noted the association of scleroderma and dermatomyositis.[47, 54, 87] Bing [6] and Friedman [31] reported cases that showed a combination of polymyositis interstitialis, scleroderma, and tendinitis calcarea.

Erysipelas, which dermatomyositis often resembles, can be excluded by the finding of the myositic phenomena such as pains and weakness.[72]

Early in the course of the disease dermatomyositis may resemble myasthenia gravis. Myasthenia gravis usually, however, runs a long chronic course—even for decades—pains are unusual and insignificant when present in myasthenia gravis, and there is a special weakness of the muscles of the face; whereas dermatomyositis runs an infinitely more rapid course, pains are an outstanding feature, and weakness of the facial muscles is absent.[5]

Oppenheim [82] has called attention to cases of polymyositis which early in their course suggested the diagnosis of "akinesia algera," spondylitis, or chronic rheumatism.

Urbach [109] described an unusual case under the name of "pseudoleukemic dermatomyositis." It resembled dermatomyositis much in appearance, but the histologic picture of areas of affected skin suggested a diagnosis of lymphoid leukemia; for there was an infiltration almost entirely of lymphocytes. However, the blood and lymph gland examinations did not support the diagnosis of leukemia.

Litten [66] found in carbon monoxide poisoning that the changes in the muscles resembled those of polymyositis. Blood examination and history will readily, however, differentiate between the two conditions.

Some believe that there is a similarity between the changes found in polymyositis and those in Volkman's ischemic myositis.[63] The history in such cases, however, will enable us to make the proper diagnosis.

Dermatomyositis may resemble that type of calcinosis or calcification of the subcutaneous tissue in which there is a sclerosis of the skin and muscle, particularly if the calcinosis is preceded by a papulo-erythematous eruption.[61]

Treatment

There is no specific treatment for dermatomyositis. Various curative and palliative measures have been suggested by different authors. Oppenheim [82] advocated diaphoresis followed by thermomassage and electrotherapy, wet packs locally, and a warm climate during convalescence. Others have suggested hot air baths,[83] repeated small doses of neosalvarsan,[55] yatren or yatren-casein injections,[32] quinine and ferric chloride,[14] and calcium chloride.[44] Tonsillectomy has often been done.[9, 15, 16, 18, 31, 55] However the results following this procedure have been discouraging. Grunke [37] employed the Leriche-Bruning's operation on the left brachial artery without any beneficial effect. Stimulation and artificial feeding, as through a tube, are frequently necessary.[57, 88]

Summary

A case of dermatomyositis with complete autopsy findings is reported. This case is of special interest because of the following: (1) involvement of the esophagus with difficulty in swallowing; (2) ulcerations of the esophagus and large intestine; (3) neurotrophic changes in the nerve ganglia of the gastrointestinal tract; and (4) edema of the larynx and glottis with consequent difficulty in speech.

A discussion of the disease is presented in light of the observations noted in a review of the literature on the subject.

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FATAL DIABETIC COMA WITH ACUTE RENAL FAILURE*

By MAYNARD E. HOLMES, M.D., F.A.C.P., *Syracuse, New York*

SEVERAL observers have called attention to the presence of impairment of renal function in diabetic coma. Fitz [1] in 1917 demonstrated that some degree of kidney insufficiency accompanied nearly all cases of severe diabetic acidosis. Joslin [2] states that in diabetic coma oliguria and moderate nitrogen retention are common but that anuria occurs only occasionally. Warburg [3] in an admirable review of this subject emphasizes the fact that it is not generally recognized that kidney function may become very deficient in diabetic acidosis. In 1931 Labbe and Boulin,[4] after a careful review of the literature on the subject, were able to collect only 16 cases of undoubted diabetic coma with blood urea retention of over 100 mg. per 100 c.c. To this number Lyall and Anderson [5] in 1932 added six cases, making a total of 22 instances of diabetic coma with urea retention of over 100 mg. per cent, observed by fewer than 20 workers. Of the original 22 cases 14 ended fatally; and in the same series there were but six deaths among 29 cases with blood urea retention of less than 100 mg. per 100 c.c. Joslin [6] reports five cases of diabetic acidosis with blood non-protein-nitrogen retention of over 100 mg. per cent with three fatalities.

The material presented here covers five cases of fatal diabetic coma all with blood non-protein-nitrogen retention of over 100 mg. per cent, observed in the past five years. All of these cases fell properly in the class of diabetic acidosis as judged by the usual clinical and laboratory criteria, namely, excessive hyperglycemia, reduction of the alkali reserve of the plasma, glycosuria and ketonuria. All were known diabetics and were under observation during their fatal illness for from two to eight days. The ages were from 11 to 55 years. In none of the cases was there evidence of preexisting renal involvement. Respiratory infection was present in all of the cases during their illness, and while it undoubtedly was a factor in precipitating the acidosis, it did not seem to be concerned in the production of the course of events which led to the fatal termination. The temperature was normal in each case upon entrance to the hospital. All cases were handled in a similar manner; insulin was given at one to six hour intervals; carbohydrate was administered in the form of orange juice, ginger ale or grape juice by mouth, or subcutaneously in 5 per cent dextrose solution or intravenously in 10 to 50 per cent solution. Water by mouth and normal saline

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From the Department of Medicine, University Hospital, Syracuse University School of Medicine.

parenterally were given as additional fluids. Alkali was given in two cases. A résumé of the important laboratory, clinical and treatment data is given in the accompanying charts. Blood sugar determinations were made by the Folin Wu method, blood plasma carbon dioxide combining power by the Van Slyke technic, non-protein-nitrogen of the blood as outlined by Folin, urine sugar by the Benedict method and the ketone bodies by the nitroprusside and ferric chloride tests.

The striking features of this group of cases were the failure of the acidosis as exemplified by the plasma carbon dioxide combining power to clear in response to insulin therapy, and the development of evidence of renal insufficiency. The carbon dioxide combining power always remained below 30 volumes per cent despite the lowering of the blood sugar and the clearing of the ketonuria. All patients seemed to respond favorably to treatment at first and all revived for a brief period a few hours after treatment was begun, only to lapse back into a fatal stupor, and finally died in apparent uremia. Oliguria was noted in all cases and anuria, for from 6 to 22 hours,

TABLE I (Case 1)

Case 1	Urine					Blood		
Date March 1929	Sugar	Acetone	Diacetic acid	Albumin	Casts R.b.c.	Sugar Mg. per cent	N.P.N. Mg. per cent	CO_2 vol. per cent
1	++++	++++	+	++	++	444	49	10
2	+	+		+++	+++	390		10
3	+			+++	+++	160	148	10
4	+							10

Case 1	Urine	Treatment					Comment
Date March 1929	Volume c.c.	Fluid intake c.c.	Carb. Gm.	Insulin units	$NaHCO_3$ Gm.	NaCl Gm.	Female, aged 18. Diabetes few wks. Ill 3 days. Stupor 12 hours.
1	2205	5600	129	220		22	B.P. 102/90. Temp. 98.8° F. Emesis 240 c.c.
2	563	4800	242	135	25	10	Talked in a.m. Emesis 480 c.c. B.P. 160/90.
3	244	6680	403	60	42	48	Talked to family. B.P. 134/60. Anuria 12 hours. Edema noted. Coma late in day.
4	0	2000	177	35			B.P. 146/42. Coma and anuria. Edema marked. Died 9 a.m.

TABLE II (Case 2)

Case 2	Urine					Blood		
Date Febr. 1929	Sugar	Acetone	Diacetic acid	Casts R.b.c.	Albumin	Sugar Mg. per cent	N.P.N. Mg. per cent	CO_2 Vol. per cent
12	++++	++++	++			412	45	10
13	+	0	0		++	153		
14	+					208		
15	++	0	0	++	+++	216		14
16	++							
17	++			+++	+++		120	16

Case 2	Urine	Treatment					Comment
Date Febr. 1929	Volume c.c.	Fluid Intake c.c.	Carb. Gm.	Insulin units	$NaCO_3$ Gm.	NaCl Gm.	Female, aged 29. Diabetes 3 mos. Ill 48 hours. Coma 13 hours.
12	600	5460	94	110		27	Temp. 97° F. Anuria 11 hours.
13	390	5370	370	60			Emesis 810 c.c. B.P. 90/70, 110/70.
14	510	2385	244	40	8		Emesis 480 c.c.
15	630	2550	200	40	24		Brighter. Talked.
16	390	1750	130	30	8		Refused food. Stupor.
17	180	2250	104	80		18	Can not arouse. Died 4 p.m.

in four individuals. Casts and red and white blood cells were present in the urine of all patients. Albuminuria, although slight at first, increased as the coma progressed. The non-protein-nitrogen of the blood, while not markedly elevated early, gradually mounted in each case until before death it exceeded 100 mg. per 100 c.c. In case 5, the blood non-protein-nitrogen was 300 mg. per cent on the eighth day which, I believe, is higher than that in any similar case as yet reported. Edema was noted in three instances toward the end, and convulsions (hypoglycemia not present) developed in one patient.

While moderate amounts of acetone were present in the urine of all cases, diacetic acid was absent in one and present only in small amounts in the urine of the other four patients. Warburg [3] calls attention to the fact that in cases of this type hyperglycemia may be marked and glycosuria and ketonuria slight, caused apparently by impairment of kidney function. Coburn [8]

TABLE III (Case 3)

Case 3	Urine					Blood		
Date Jan. 1934	Sugar	Acetone	Diacetic acid	Casts R.b.c.	Albumin	Sugar Mg. per cent	N.P.N. Mg. per cent	CO_2 vol. per cent
30	++++	+++	0	+++	+++			
31	++++	+	0	+++	+++	395	105	15

Case 3	Urine	Treatment				Comment
Date Jan. 1934	Volume c.c.	Fluid intake c.c.	Carb. Gm.	Insulin units	NaCl Gm.	Male aged 28. Diabetes several months. Ill 4 days.
30	105	3260	47	120	18	Temp. 97.6° F. Anuria after 11 p.m.
31	0	2950	51	0	18	Anuria. Died 8 a.m.

has also stressed the point that severe ketonemia may be present despite the absence of acetone bodies in the urine. In Rabinowitch's [9] case, however, the blood serum gave a negative response to the Wishart test for acetone. Starr and Fitz,[10] and Bock [11] report the presence of some unidentified organic acid in the blood of cases of diabetic coma in which the plasma CO_2 combining power fails to rise under adequate insulin therapy, a non-ketone acidosis. Values for the blood non-protein-nitrogen and other evidence of renal involvement were not given for these cases.

The increase in the blood non-protein-nitrogen is probably not entirely an index of failure of kidney function since concentration of the chemical constituents including urea is brought about by dehydration always present in severe diabetic coma. However in this series, the grade of nitrogen retention was much greater than that reported [13] as a result of dehydration, and the retention occurred late after the anhydremia had apparently been overcome by the administration of large amounts of fluids. The presence of oliguria, anuria, albumin, casts and red blood cells in the urine, edema, and in one patient convulsions can leave little doubt that the severe azotemia in these cases was due to direct retention as a result of acute functional renal failure.

Several factors have been suggested as being concerned in the development of this type of renal failure: (1) shock, (2) dehydration, (3) disturbance of the plasma electrolytes, (4) increased destruction of endogenous protein, (5) insulin and (6) pathologic change in the kidney. Most of these factors are probably interrelated.

Shock in various degrees of severity accompanies all cases of severe

TABLE IV (Case 4)

Case 4	Urine					Blood		
Date Sept. 1932	Sugar	Acetone	Diacetic acid	Albumin	Casts R.b.c.	Sugar Mg. per cent	N.P.N. Mg. per cent	CO_2 vol. per cent
8	++++	+++	+	++	+	480		
9	++			+++	+	400	103	21
10	++	0	+	+++	++	182	120	
11	++					206	114	22

Case 4	Urine	Treatment				Comment
Date Sept. 1932	Volume c.c.	Fluid intake c.c.	Carb. Gm.	Insulin units	NaCl Gm.	Female, aged 55. Diabetes 4 yrs., on insulin. Ill and no insulin 4 days. Coma 18 hours.
8	150	3380	145	290	27	Temp. 97.4° F. No edema. Anuria 12 hours. 500 c.c. 10 per cent dextrose by vein.
9	105	4100	75	230	36	B.P. 140/70. Edema noted. Anuria 10 hours. 750 c.c. 10 per cent dextrose by vein.
10	112	4600	200	180	39	B.P. 140/80. Emesis 90 c.c. Anuria 22 hours. 300 c.c. 25 per cent dextrose by vein. Edema increased.
11	510	3500	200	130	27	B.P. 140/80. Voided 510 c.c. after 11 p.m. 300 c.c. 25 per cent dextrose by vein. Edema marked. Died 2 a.m. Sept. 12.

diabetic coma. Dehydration, caused by loss of fluids and electrolytes from the blood, produces a condition of hemoconcentration. The resultant diminished blood volume, lowered blood pressure and capillary stasis combine to produce a condition of general vasomotor collapse.[12] Failure of the capillary circulation of the kidney follows with impairment of renal function, oliguria, anuria, and finally nitrogen retention.

That nitrogen retention may occur as a result of dehydration incident to low fluid intake, and excessive loss of fluid by polyuria, vomiting, sweating and hyperpnea, has been demonstrated by Bulger and Peters.[13] Further loss of fluids may occur by transudation from the blood vessels into the tissues.[14] Additional evidence that azotemia may be related to disturbance of the blood electrolyte are the observations of Blum,[15] who in two cases of diabetic coma after partial recovery was able to produce marked nitrogen retention by restricting the chloride intake for six days. When salt was

TABLE V (Case 5)

Case 5	Urine					Blood		
Date March 1931	Sugar	Acetone	Diacetic acid	Casts R.b.c.	Albumin	Sugar Mg. per cent	N.P.N. Mg. per cent	CO_2 vol. per cent
26	++++	++++	++	++	++	440	39	30
27	+	+	+			230		
28	+	+	+	++	++++	133	99	
29	+							
30	++			++				
31	++					487 160	114	29
1	++			++	++++	542 96	171	20
2	++				++++	160 90	223 300	9

Case 5	Urine	Treatment				Comment
Date March 1931	Volume c.c.	Fluid intake c.c.	Carb. Gm.	Insulin units	NaCl Gm.	Female, aged 11. Diabetes 4 yrs., on insulin. Ill and no insulin 1 week.
26	75	2290	146	50	16	Stupor 12 hrs. Temp. 97° F.
27	34	2840	112	60	9	Emesis 400 c.c.
28	165	3160	117	0	18	Answers questions. 50 c.c. 25 per cent dextrose by vein
29	120	1265	70	20		Myringotomy, emesis 60 c.c. Hungry, edema noted. 50 c.c. 25 per cent dextrose by vein.
30	225	2215	104	25	14	Emesis 120 c.c., edema noted.
31	165	1610	100	35	14	B.P. 125/100, convulsions. Spinal fluid negative. 50 c.c. 25 per cent dextrose by vein.
1	225	775	63	20	7	Convulsions, edema marked. 25 c.c. 25 per cent dextrose by vein.
2	210	50	25	15		50 c.c. 25 per cent dextrose by vein. Edema marked. Died 3 a.m. Apr. 3.

again administered, the blood urea was restored to a normal level. In a third case under the same régime he was unable to produce azotemia. Depletion of the blood chlorides has been noted in diabetic acidosis. Peters [16] emphasizes that in severe diabetic toxemia the salt content of the blood may be seriously depleted by the loss of chloride to furnish base to neutralize the organic acids present. There is also increased excretion of salt in the urine because of the severe glycosuria.[12] Hartmann [17] believes that in the presence of hypochloremia there occurs an increase in the non electrolyte urea to compensate osmotically for the loss of chloride and carbonate from the blood. Hypochloremia, however, apparently is not a constant finding in diabetic coma with acute renal block, as the cases reported by Fitz,[1] Bulger and Peters,[13] Fullerton [18] and Lyall and Anderson [5] revealed normal or increased blood chloride levels. While hypochloremia may occasionally be the primary cause in the production of azotemia in severe diabetic coma, it probably is more commonly concerned only as it contributes to the general state of dehydration.

Excessive breakdown of endogenous protein is said to occur in diabetic acidosis.[5] Atchley [19] noted increased nitrogen excretion in his cases following the withdrawal of insulin. Dehydration which is present in all cases of severe diabetic coma is often accompanied by marked destruction of body protoplasm.[20, 21] This process may be concerned in the production of azotemia in severe diabetic acidosis in the same manner that it is believed to cause nitrogen retention in high intestinal obstruction.

There are many points of similarity between diabetic coma with acute renal failure and the toxemia of high intestinal obstruction. Shock, vomiting, dehydration, oliguria, anuria, nitrogen retention and hypochloremia have been noted in both conditions. The same processes believed to be concerned in the production of the azotemia of obstruction may also be operating in severe diabetic acidosis.

The possibility that insulin may be a factor in the production of nitrogen retention in diabetic coma has been suggested by Joslin [2] and by Bayer [22] who reports a fatal case receiving 1145 units during six and a half days. However, the more commonplace explanation is that these large doses were necessary because of the extreme grade of the acidosis present and that it is in such cases that nitrogen retention is most likely to occur. Moreover, urea retention was noted in fatal cases of diabetic coma before insulin was introduced.[1]

That some degree of nephropathy is present in the majority of instances of diabetic coma is indicated by the presence of albumin, casts and red blood cells in the urine. Actual parenchymal renal damage probably results from the excessive excretion of ketones, acids and other metabolites. MacNider [23] demonstrated in dogs that the introduction into the blood of either acid or alkali in amounts sufficient to alter the physico-chemical state of the blood to a degree that readjustment was impossible, caused severe renal insufficiency to develop, and the kidneys at autopsy revealed changes similar to

those reported in fatal diabetic coma with acute renal failure. The pathologic changes found in the kidneys of patients dying of diabetic acidosis with renal insufficiency have been described by Warburg,[3] Snapper,[24] Labbe,[4] Bayer,[22] and Kraus.[25] The lesions found have been designated as a nephrosis and also as an early acute nephritis; the kidneys are large and pale with edema of the stroma, and degenerative changes in the tubular epithelium are a prominent feature. Coburn [8] found no evident renal change in two of his cases which came to autopsy; these cases were observed only a few hours, and evidence of nitrogen retention or of the urinary findings of renal disease was not given. Joslin [6] reports two fatal cases of this type with multiple abscesses of the kidney.

The treatment of diabetic coma with acute renal failure is likely to be discouraging in the majority of instances especially if nitrogen retention of any marked degree is present. Coburn [8] emphasizes the importance of blood transfusion and of the intravenous administration of hypertonic solutions of glucose and alkali. Fullerton [18] reports a case with a blood urea above 100 mg. per cent that recovered after the administration of hypertonic dextrose solution intravenously. In case 4 of this series after anuria of 22 hours, there was an excretion of 510 c.c. of urine on the final day apparently as a result of the giving of hypertonic dextrose solution by vein, but in case 5 it had little or no effect. Root [26] successfully treated three cases with blood non-protein-nitrogen retention of over 100 mg. per cent, with hypertonic salt solution intravenously. He believes that hypochloremia is an important causative factor in this condition, although in one case recorded the blood chlorides were 463 mg. per cent. John [27] describes a case with severe azotemia that recovered after the administration of Fisher's solution by vein. The use of alkali has been advocated in diabetic coma by Starr and Fitz,[10] Bock,[11] Hartmann,[28] Marriott,[29] Bowen [30] and others, and its use opposed by Joslin,[6] Peters,[16] Lemann [31] and others. In cases 1 and 2 of this series alkali was given but without apparent effect either clinically or chemically. Present experience would seem to indicate that oliguria, anuria and nitrogen retention in diabetic coma can best be combated by overcoming the dehydration and hemoconcentration present with large amounts of normal saline given in part intravenously. Hypertonic salt solution should be administered by vein especially if hypochloremia is present and intravenous infusions of hypertonic dextrose solution given particularly if hyperglycemia is not marked. In the presence of hypotension and shock, fluids and insulin should for the most part be given by vein. When other methods fail to relieve shock and anuria there is justification for the use of blood transfusion.[15]

Summary

Five cases of fatal diabetic coma with acute functional renal failure have been reported, with clinical, laboratory and treatment data. The possible explanations for this type of kidney insufficiency have been discussed.

Its development would seem to depend on the following sequence of events; depletion of water and electrolyte from the blood incident to diabetic acidosis, bringing about a condition of dehydration and hemoconcentration with diminished blood volume and hypotension. A state of so-called shock follows with failure of the capillary circulation of the kidney, impairment of renal function, oliguria, anuria, and finally nitrogen retention. In the cases with nitrogen retention of any marked degree actual pathologic changes in the kidney parenchyma develop and become the important factor in the insufficiency. The prognosis in diabetic coma with marked nitrogen retention must be guarded; some patients will recover after exhibiting symptoms of uremia while others progress to a fatal termination in spite of all treatment.

For permission to report these cases the author is indebted to Dr. Edward C. Reifenstein, Professor of Medicine and Director of the Medical Service of the University Hospital, Syracuse University School of Medicine.

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INCIDENCE AND SIGNIFICANCE OF THE ROENTGENOLOGIC NICHE IN DUODENAL ULCER *

By B. R. KIRKLIN, M.D., F.A.C.P., and H. A. BURCH, M.D.,
Rochester, Minnesota

IN 1911, at the fortieth assembly of the German Surgical Society, Martin Haudek mentioned the niche as one of the roentgenologic signs of duodenal ulcer, and in a formal paper published in 1912 he cited among several cases four in which niches were demonstrated. In these cases the crater of the ulcer was depicted by a small deposit of bismuth which could scarcely be displaced by manipulation and corresponded to a point on the abdomen that was sensitive to pressure. Although his descriptions and drawings were convincing, the new sign of duodenal ulcer apparently received little attention, and the diagnosis continued to be based chiefly on clinical symptoms in combination with roentgenologic signs of hypermotility and other secondary manifestations. In 1914, Lewis Gregory Cole placed the diagnosis on the logical, practical, and substantial basis of bulbar deformity caused by induration or cicatricial contraction resulting from the ulcer. On that occasion he said also that in some instances the bismuth-filled crater of the ulcer could be seen in profile or face. But distortion of the bulb proved to be such a constant and reliable sign that most examiners still regarded the niche as a mildly interesting but relatively unimportant detail.

Not until 1923, when Akerlund reported an incidence of 60 per cent of niches in more than 100 cases of duodenal ulcer, was this sign given more than passing consideration. Since then various computations as to the frequency with which a niche can be demonstrated have appeared, such as those of Diamond, 66.6 per cent; Carman and Sutherland, 13.27 per cent; Berg, 50 per cent; Albrecht, 90 per cent; Akerlund, 75 per cent (in 1931); Kirklin, 15.24 per cent; Geyman, 64 per cent; Clark and Geyman, 54 per cent; Ettinger and Davis, 50 per cent. For comparison with these estimates we have again reviewed the records of this clinic for the 15 months ending March 31, 1935. During that period duodenal ulcer was diagnosed roentgenologically in 1,489 cases, and the presence of a niche was noted in only 264, or 17.7 per cent. The marked discordance in these statistics led us to inquire further into the problem of incidence, not with the expectation of solving it decisively, but with the hope of finding probable reasons for some of the discrepancies.

Diverse conceptions of the criteria by which the niche should be judged probably underlie the entire disparity of incidence. It is generally agreed that, depending on the angle of view, niches may be marginal (figure 1) or central (figures 2 and 3); that they are more often situated on the mesial

* Read before the Philadelphia meeting of the American College of Physicians, May 1, 1935.

From The Mayo Clinic, Rochester, Minnesota.

border or posterior or anterior wall of the bulb, but may occur in the base or lateral wall or in the descending portion of the duodenum (figure 4); that usually they are small, with a diameter from one or two mm. to one cm.; that they may be hemispherical, angular or irregular in profile, and that an individual niche should maintain the same site and form during the examination and at reëxamination. To these characteristics we would add, as would other examiners who depend primarily on roentgenoscopy for diagnosis, that the deposit of barium in the crater should persist for a time, not only when the bulb is evacuated spontaneously or by steady pressure, but also and especially when the bulb is subjected to palpatory manipulation.

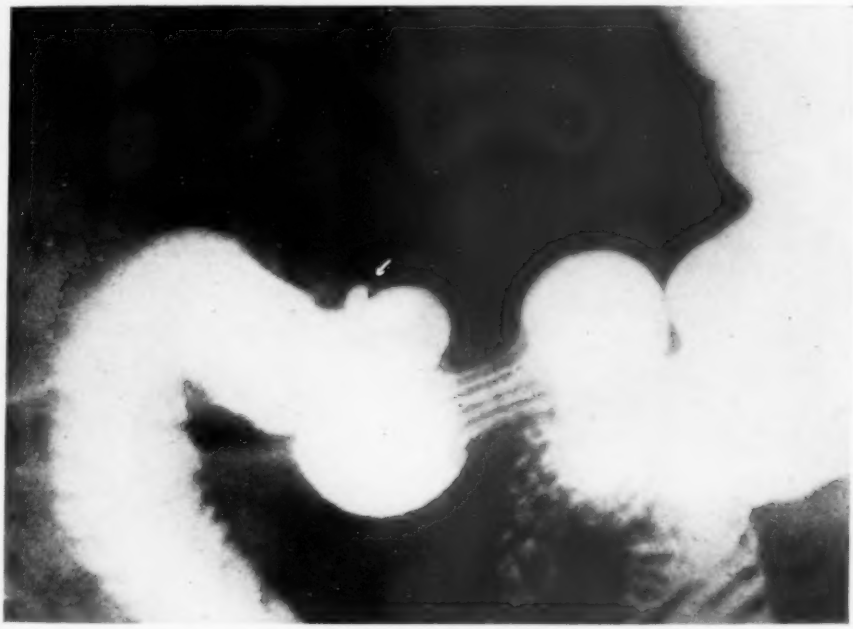

FIG. 1. Marginal niche on lesser curvature side of bulb.

This immediately brings up the collateral question as to the technic that should be employed. Most of those examiners who have found a high percentage of niches employ roentgenography with the well known compression apparatus as a routine, and they insist that many small niches will otherwise escape roentgenoscopic observation. But, even if it is conceded that roentgenograms will depict minute niches that cannot be seen on the fluoroscopic screen, the roentgenographic method introduces a new factor of error in the opposite direction. In the many cases of duodenal ulcer, whether temporarily healed or active and with or without a definite crater, in which the bulb presents multiple spastic or cicatricial sacculations or a pseudodiverticulum, any or all of the pouches may retain barium under the steady pressure employed in the roentgenographic method and may be mistaken for

niches. Moreover, by this method a small aggregation of barium may be pent up in the pyloric canal or in the mucosal folds of a normal bulb and thus simulate a niche. On the other hand, by roentgenoscopy with manipulation, practically all pseudoniches can be emptied and by this feature distinguished from true niches.

At the clinic, compression roentgenography is often employed to depict duodenal niches and other phenomena of which a permanent record is desired. In our hands this method has not as yet disclosed any niche which had not been discerned roentgenoscopically. However, any examiner who is at all doubtful as to the reliability of his roentgenoscopic technic is quite justified in using compression roentgenography as a routine.

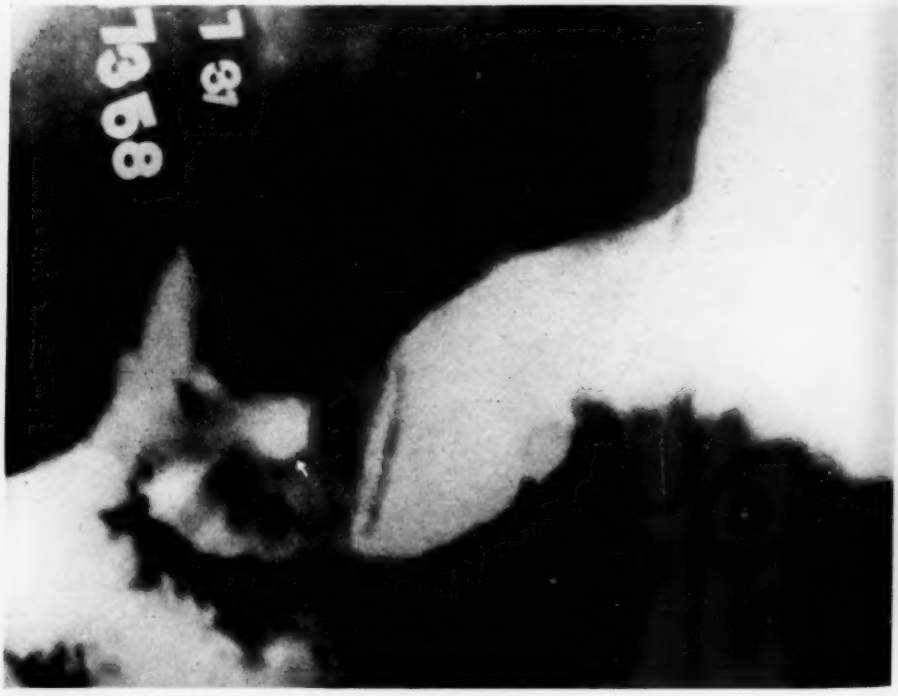

FIG. 2. Large central niche appearing on pressure.

Differences in bases of computation may also account for some of the variances. All estimates from the clinic, including those of Carman and Sutherland (13.27 per cent of niches), those of Kirklin (15.24 per cent), and the present computation of 17.7 per cent, represent the ratio of cases in which a niche was discerned to the total number of cases in which duodenal ulcer was diagnosed roentgenologically. It is true that by no means all of these diagnoses had been confirmed surgically or otherwise, for the larger proportion of the patients were not operated on, and in a great number of cases the ulcers undoubtedly were healed at the time of examination. But,

at this clinic, errors in the roentgenologic diagnosis in cases in which patients were operated on have not for many years exceeded 5 per cent, hence it was considered fair and reasonable to take the entire number of diagnoses as a basis for calculating the percentage of niches seen with roentgen-rays. Further, the patients were not a selected group with such marked gastroduodenal symptoms that positive roentgenologic data could be expected, but many patients were included whose symptoms were vague, trivial, or ancient and for whom the examination was ordered as a routine to exclude organic disease of the digestive tract. Thus it is safe to assume that healed

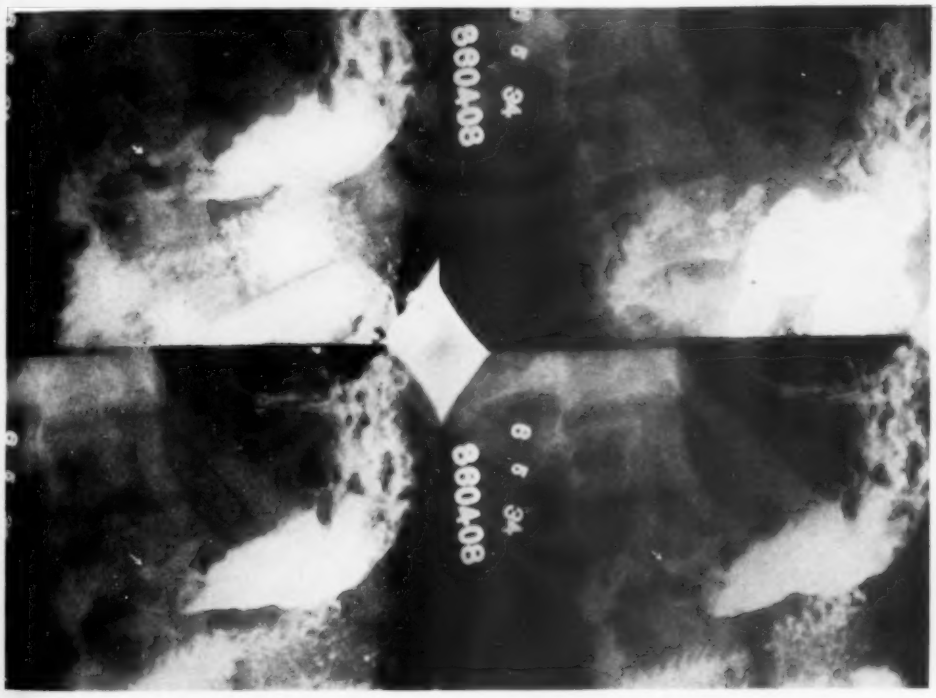

FIG. 3. Central niche, constant in all four views.

ulcers predominated over those that were active and that ulcers with craters were decidedly in the minority.

Akerlund's estimate, in 1931, of 75 per cent of niches was based on "cases of ulcer definitely established radiologically," Geyman's 64 per cent on "bulbs having deformity characteristic of duodenal ulcer," and Clark and Geyman's 54 per cent on "all cases of duodenal ulcer." In contrast with these, Berg's 50 per cent was based on "all cases proved by operation," and Diamond's statements indicate that his 66.6 per cent was also derived from surgically proved cases. Ordinarily, patients having duodenal ulcer are not subjected to operation unless symptoms and signs are severe, and such patients are likely to have a relatively high ratio of active ulcers with

craters capable of demonstration as niches. It is noteworthy, however, that equally high or higher percentages of niches were found by some of the observers in patients in whom roentgenologic evidence of an ulcer was conclusive but many of whom presumably were not operated on. But this apparent inconsistency should not be overemphasized, for the basic groups that included nonsurgical cases may have comprised chiefly patients who had pronounced symptoms and hence probably had a large proportion of active, crateriform ulcers. As an instance in point, we reviewed the first 100 cases of clinically active duodenal ulcer encountered in the roentgeno-

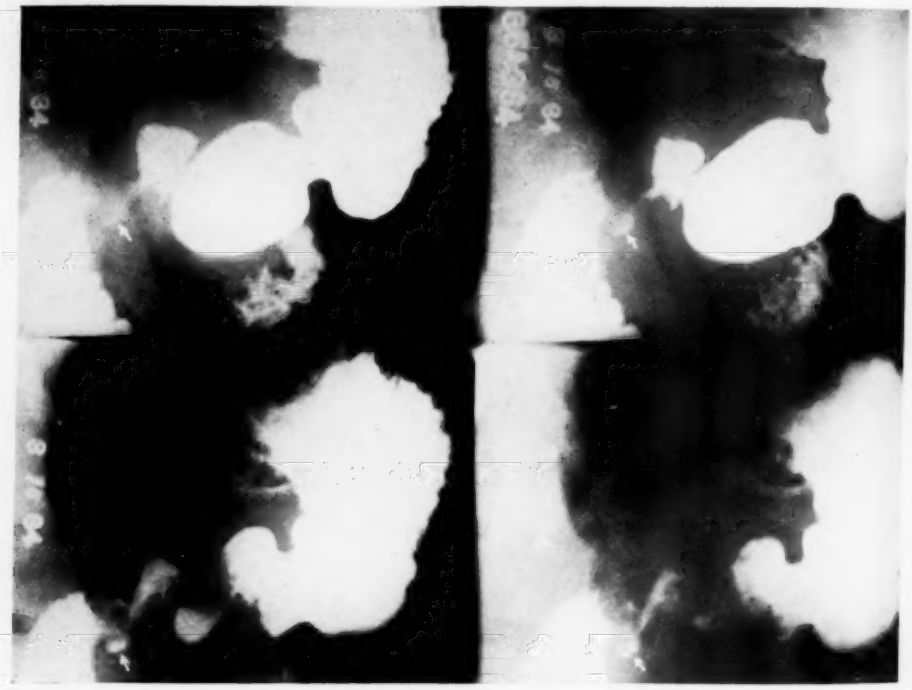

FIG. 4. Large niche in second portion of duodenum.

logic section of the clinic this year. In each of these cases the syndrome, with or without signs of hemorrhage, was so emphatic at the time of examination that the clinician regarded the lesion as active, and a roentgenologic niche was discerned in 38 of the 100 cases. In other words, the incidence of crateriform ulcers in this selected group of cases is twice as high as in the unselected group.

To obtain anatomic data on the incidence of the niche, we have studied 176 ulcers taken at necropsy from 140 subjects during the period from January 1, 1931 to January 1, 1934. Among the 140 subjects, 67 had healed ulcers only, 14 had both healed and active ulcers, and 59 had active ulcers only. In 66 of these 67 cases of healed ulcers alone no pit remained

at the site of the lesion; in only one was there a minute depression which might have been construed as a niche at roentgenologic examination. Of the 73 cases in which ulcers had been active (14 plus 59) there were definite craters in thirty-six. Thus craters probably demonstrable as roentgenologic niches during life were present in 37 of 140 subjects, or 25.4 per cent. Of the 73 with active ulcers, if this group is taken as a basis, slightly less than 50 per cent had ulcer craters that were potentially demonstrable as niches. On the other hand, of the 176 ulcers, comprising healed, active, combined, and multiple lesions, only 40, or 22.7 per cent, were capable of exhibition as roentgenologic niches.

This low anatomic incidence is consonant with the still lower roentgenologic incidence observed at the clinic, for the roentgenologist cannot discover all existing craters. Our data are not presented as being decisive. It could be argued that an apparently craterless ulcer in a cadaver might have produced a demonstrable roentgenologic niche during life, when the tissues were engorged and the contractile tonus of the muscularis mucosa was present. It could also be argued that subjective elements entered into judgment as to the presence or absence of a crater, although every effort was made to avoid prejudice and to resolve doubts in favor of the presence of a niche. In fact, conclusive statistics as to the frequency with which niches occur can scarcely be obtained, for in every case it would be necessary to show that the roentgenologic niche corresponded precisely to a crater disclosed at operation or at necropsy, and even here the personal equation would enter. So, although for the reasons cited we adhere to the belief that the actual incidence of the niche in material comparable to ours is low, we do not question the skill or competence of observers who report high percentages. Indeed, we would be glad if we could confirm their opinion, for the niche is an important item in the diagnosis of ulcer.

Significance of the Niche

Roentgenologically, the niche has a threefold significance, for it is an important sign of ulcer, indicates that the ulcer is active, and is a valuable criterion in appraising the effect of treatment.

A definite niche is pathognomonic of ulcer, and the only sign that is pathognomonic. Occasionally a niche is the sole sign, and in all other respects the duodenum is normal (figure 5). Usually, in such cases, the niche appears as a comparatively dense fleck internal to the bulbar contour when the duodenal walls are approximated by compression. Further, when the bulb presents multiple sacculations, it is seldom safe to assume that any particular recess is the crater of an ulcer unless a corresponding internal or marginal fleck persists under manipulation, and an incisure opposite a marginal recess is much less convincing evidence that the recess is the crater of an ulcer. Another rare and striking variety of niche is the accessory pocket produced by a perforated ulcer with excavation into the pancreas or

liver. The more or less rounded cavity fills with barium and the narrow channel leading to the duodenum is usually depicted. These tributes to the niche do not detract from the general reliability of duodenal deformity as a sign of ulcer. Simulants from other causes are well known and can usually be identified, and if reliance could not be placed on deformity, a large proportion of ulcers would escape recognition. The only shortcoming of this sign is that by deformity alone active ulcers cannot be distinguished from those that are healed.

The niche is practically an unequivocal sign that an ulcer is active, for

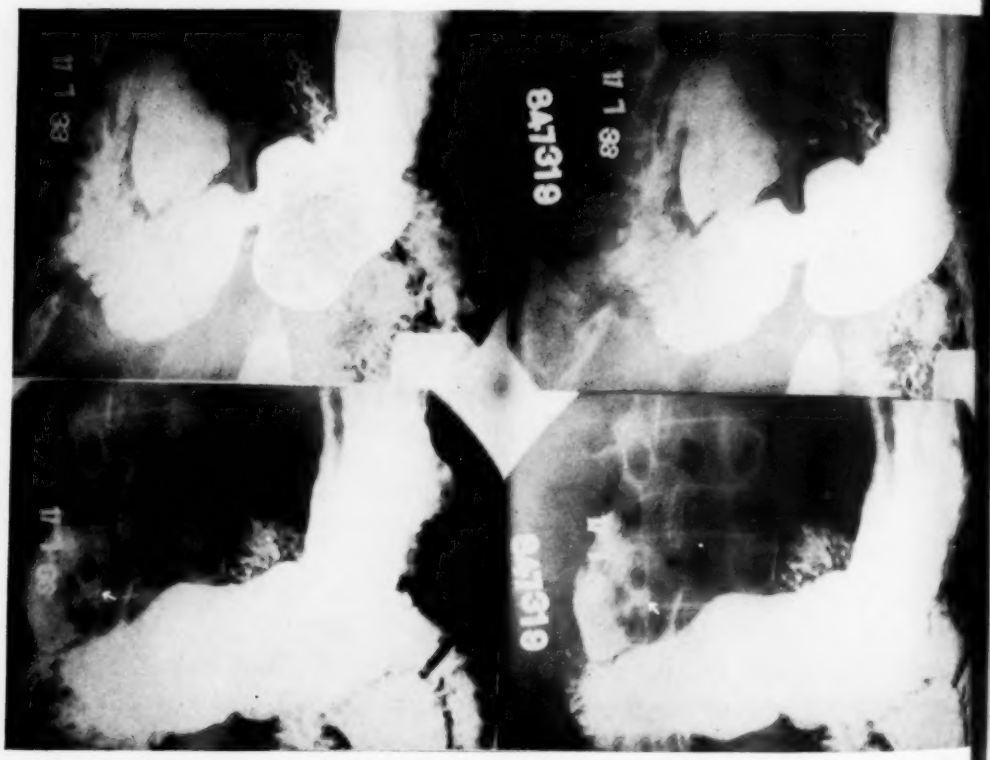

FIG. 5. Large central niche depicted in two lower views under pressure; in the two upper views, made without pressure, the bulb appears to be normal.

healed ulcers with demonstrable depressions are so rare that they can be disregarded. But the niche is not the sole sign of activity. Increased irritability of the bulb, as shown by rapid emptying and quickly changing contour, is an equally trustworthy index. Often, in addition, the internal relief has the diffusely mottled appearance characteristic of duodenitis, and the activity of the process cannot be doubted. When the bulb is deformed, but a niche cannot be discerned and marked irritability or evidence of duodenitis is also absent, it is the custom at the clinic to return a roentgenologic

diagnosis of ulcer and leave to the clinician the task of determining whether it is probably active or healed.

In determining the response of an ulcer to treatment, the niche is a factor of moment. If the niche diminishes or vanishes, it is indicative of progress toward cure. But disappearance of the roentgenologic niche does not necessarily signify that the ulcer has healed. Roentgenologists agree that florid ulcers often have no discernible craters. Mann has shown that the craters of experimentally produced peptic ulcers in process of healing gradually fill with granulation tissue, and that by proliferation of the marginal mucosa the granulation tissue is forced out of the crater like a plug. These observations accord with the cited ratio of craters in active ulcers found at necropsy and support the opinion that in the usual series of patients having healed, partially healed, and florid ulcers, niches would scarcely be demonstrable in more than 25 per cent of cases.

Whatever its incidence may be, the niche should be sought for diligently at every examination, for it is incumbent on the roentgenologist not only to discover existing ulcers, but also to furnish all available information concerning their activity.

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PERSONALITY AND THE ENDOCRINES; A STUDY BASED UPON 1400 QUANTITATIVE NECROPSIES *

By WALTER FREEMAN, M.D., F.A.C.P., *Washington, D. C.*

IN recent times there has been intensive study of the excesses and deficiencies of the glands supplying hormones to the body, and a multitude of clinical syndromes have been described. It is now possible, on the basis of structural and biochemical studies, to identify disturbances in a number of these glands. When it comes to personality studies in relationship with the endocrine system, however, there is a school of thought which, in the quaint words of Benjamin Franklin [1] concerning the medical school in Edinburgh, "seems better calculated to please the fancy than to form the Judgment." The Italian school of constitutional pathologists under Viola [2] probably started this trend of thought, but, like many another imported plague, the idea became pandemic, and reached its acme in Berman's book, "The Glands Regulating Personality." [3] At the present time the antivirus of common sense, aided by truly scientific researches, has brought about a better balance, so that Hoskins [4] can write: "To those who, in the present state of our knowledge, would glibly re-write physiology and psychology in terms of pituitary functions the timorousness of the proverbial angel is commended."

THE PERSONALITIES

In previous communications presented before this College [5, 6] four fundamental personality reaction types have been described: cycloid, paranoid, schizoid and epileptoid. The individual of cycloid temperament is extraverted, industrious, subject to fluctuations in mood, athletic and highly sexed. The paranoid individual is reserved, suspicious, antagonistic, embittered and calculating. The schizoid patient is introverted, retiring, self-deprecatory, studious, meticulous and low in physical vitality. The epileptoid individual is moody, pedantic, devout, and subject to paroxysmal headaches, rages, fits. When any person suffers a sufficient exaggeration of one of these trends (which may be found in all people) he becomes dangerous to himself or others and requires psychiatric care. It has further been emphasized in the previous studies that these underlying personality reactions may become exaggerated not only as the result of some as yet obscure etiology resulting in the so-called major psychoses, but also as the result of organic disease of the brain such as senility, syphilis, arteriosclerosis, and the like. When the controlling balance of the mind breaks down, the in-

* Read at the Philadelphia meeting of the American College of Physicians, April 29, 1935.

From Blackburn Laboratory, St. Elizabeth's Hospital, and the Department of Neurology, George Washington University, Washington, D. C.

dividual's personality deviates more or less in one or another of the directions enumerated above, cycloid, paranoid, schizoid, or epileptoid. This is the reason why material from psychotic patients offers such a splendid opportunity for the investigation of various somatic factors involved in the genesis and determination of the personality of the individual. If it can be shown, for instance, that those who show a paranoid trend have large suprarenal glands and small thyroids, some insight may be gained into the mechanism of personality. A biometrical study [7] that will shed light on this question is now under way. In a recent paper dealing with the weight of the endocrine glands,[8] I concluded with the apologia: "In defense of this method of approach to the study of mental disorders, it may be said that if statistically significant differences are found in the glands of men who behave differently, even though due allowances are made for age, sex, race, weight, and stature, then these differences will assume an importance far beyond the few grams, or milligrams even, that may separate their mean weights."

The Material

During the past 10 years, psychotic patients dying at St. Elizabeth's Hospital have been submitted to quantitative necropsy, even the pineal and parathyroids being removed and weighed before being studied histologically. Moreover, in most of the cases it has been possible to obtain photographs of the body beforehand so that growth disorders and constitutional types might be determined. The material has been classified into the four personality types irrespective of the etiology of the mental disorder by my colleague, Dr. Nolan D. C. Lewis.

For the purpose of this study I have selected from the material cases showing the most marked deviations in the weight of the individual endocrine glands with the possibility in mind that there might be a general family resemblance, so to speak, among those possessing, say, large normal thyroids, which might be contrasted with the characteristics of a group showing small thyroids.

The dangers of too implicit reliance upon postmortem data cannot be too frequently reiterated. Nevertheless, until the time comes when clinical assay of active endocrine principles in the circulating blood becomes possible, the method of pathologic anatomy must receive due consideration. Too many patients with outspoken diabetes have been found to possess an abundance of normal islet tissue, and too many patients with sclerosis and hyalinization of the islets of Langerhans have been innocent of glycosuria to make it axiomatic that diabetes mellitus is a disease only of the pancreas. In all probability there are large factors of safety in each endocrine organ, and also, as has been abundantly proved, interrelationships among the glands that balance one against the other.

The biometrical method is empirical: let us examine the results.

Large Glands and Small Glands *

Epiphysis. The pineal gland averages between 150 and 185 mg. in weight. Twenty-six patients, with glands weighing 400 mg. or over, were compared with 24 patients carrying glands weighing less than 50 mg. No differences whatever could be observed in the trend of the personality.

Hypophysis. The important sex differences in the pituitary gland make it advisable to consider males and females separately. In the male the gland averages from 690 to 730 mg. in weight. Twenty men with pituitaries weighing over 1000 mg. were compared with 14 men in whom the pituitary weighed 400 mg. or less. The material is small but the proportionate representation of each of the personality reaction types is almost exactly that of the whole group of 1400 cases. In the female, the average weight of the gland is from 760 to 815 mg. Fifteen women, with glands weighing 1100 mg. or more, were compared with 21 possessing glands weighing 500 mg. or less. From the standpoint of personality there is a little higher incidence of manic-depressive temperament (cycloid personality) in those possessing large pituitaries, while an unusually large percentage (4 out of 21 cases) of those with small hypophyses were undifferentiated as to personality. From this it may be inferred that the pituitary supplies an energy drive that enables the personality to unfold. There is little evidence that it determines the personality, since the great groups of schizoid and paranoid personalities are almost perfectly balanced.

Thyroid. The weight of the normal thyroid gland ranges, on the average, between 16 and 23 grams. Fifteen patients, with healthy thyroids weighing 50 grams or more, were compared with 21 patients in whom the gland weighed less than 8 grams. The material is quite small, but again there is an undue proportion of patients with undifferentiated personalities among the " small-thyroid " group, and a correspondingly large representation of the cycloid group in those bearing large thyroids. It is quite striking that 10 of the 22 " small-thyroid " patients had pituitaries weighing 500 mg. or less.

In view of the relationship emphasized by Hoskins between thyroid deficiency and dementia precox with its predominant schizoid tendency, special attention was given to the presence of small thyroids in association with schizoid personalities. In the females, this association was quite suggestive, but in the males the opposite trend was observed. It seems likely that the driving force of the thyroid is of importance in developing the personality rather than in orienting it in any particular direction.

Parathyroids. The parathyroid glands average from 145 to 170 mg. in weight. Thirty-one patients, with glands weighing 300 mg. or more, were compared with 21 patients with glands weighing 50 mg. or less. In

* The averages given are those obtained in the previous study [8] the two figures representing the upper and lower figures for sex-race combinations. For instance in the case of the pineal the figures are: white male, 172 mg.; colored male, 151 mg.; white female, 183 mg.; colored female, 157 mg.

view of the suspected relationship between hypoparathyroidism, tetany and epilepsy, it was illuminating to find two epileptics with large parathyroids, and one with small parathyroids. Furthermore, with regard to the known irritability of the nervous system in parathyroid deficiency, it was unexpected to find the aggressive paranoids and submissive schizoids exactly balanced. There was a moderate percentage of cycloid individuals with large parathyroids, while this temperament was disclosed only once among those having unusually small parathyroids. On the whole, it must be concluded that the parathyroids are of little importance in the fundamental personality trend of the individual.

Thymus. The thymus averages from 12 to 18 grams in weight. It is extremely susceptible to changes in nutrition so that the weight of the gland is of relatively little importance. On the other hand, there is ordinarily an involution of the parenchymatous elements, so that in this gland the percentage of lymphoid tissue has been correlated with personality type. Thirty-two patients with thymus glands presenting 20 per cent or more of parenchymatous tissue were compared with 42 patients in whom the thymus tissue was reduced at most to a few strands. The outstanding feature was the high proportion (44 per cent) of epileptoid personalities in the persistent thymus group, whereas in the whole number of cases, the epileptoids account for only 8.6 per cent. There were three epileptoids among the 42 cases with completely involuted thymuses. Does this mean that the thymus determines the epileptoid personality reaction? There appears to be some disturbance of the general bodily development in a fairly large number of those presenting persistent thymus glands, a softness and rounding of contours indicating possibly a positive water balance. On the other hand, the thymus is known to undergo rapid involution in response to various unfavorable conditions like infections and especially wasting diseases. Most of the epileptoids die rather rapidly when their time arrives, and as a group they are younger, so that while the association of persistent thymus and the epileptoid reaction is a pronounced one, it would be hazardous to state that epilepsy is due to persistence of the thymus gland. In any case, it should be an easy matter to provoke involution in the thymus by means of roentgen-rays in a large number of epileptics and to study the results. The schizoid and paranoid personality reactions show no differences, while individuals with cyclothymic tendencies have a little higher representation in the "small-thymus" group.

Suprarenals. The suprarenal glands average from 12.5 to 15.5 grams in weight. Twenty-three patients with glands weighing 20 grams or more have been compared with 25 others carrying glands weighing less than 8 grams. Lack of personality differentiation is again a feature of those with small suprarenal glands, six out of the 25 presenting insufficient personality characteristics to allow them to be grouped. On the other hand, among those with large suprarenals there is a slightly greater representation

of the aggressive paranoid group. The differences are too small, however, to be more than suggestive.

Testes. The weight of the testes averages from 25 to 30 grams. In this study 31 patients with testes weighing over 45 grams were compared with 18 patients in whom the testes weighed less than 10 grams. Nine of the 31 with large testes belonged in the cycloid group, while only one patient with small testes fell in the same group. As shown in a previous communication,[9] the large testis seems to be a rather general characteristic of the cycloid group. Except for this, there is no outstanding difference between the large-testis group and the small-testis group although paranoid personalities are common in the latter. The histories of these patients have not been exhaustively studied, but it is mentioned in the abstracts of three of the former that homosexuality was present, while this phenomenon was not encountered among those possessing small glands.

In contrast with the mildly suggestive findings on correlating the size of the testes with the type of personality, it seems justifiable to point to the rather pronounced somatic differences observed in these two groups, as indicated in the accompanying table.

TABLE I

Incidence of Somatic Disorders and Personality Deviations Correlated with Size of Testes

	Percentages										Personality				
	Number	Per cent	Blood pressure over 160 mm.	Circulatory deaths	Hirsutism	Bald crown	Large hips	Gynecomastia	Hairless body	Homosexuality	Personality undifferentiated	Cycloid personality	Paranoid personality	Schizoid personality	Epileptoid personality
Large testes	31	100	55	45	31	58	36	0	22	10	7	29	32	29	3
Small testes	18	100	54	5	0	11	61	17	83	0	12	6	55	22	5

Ovaries. The ovaries average four to five grams in weight. A group of 15 women whose normal ovaries weighed more than 10 grams was compared with another group of 27 women whose ovaries weighed less than 1.7 grams. Aside from a comparatively low incidence of paranoid individuals among those possessing large ovaries, no outstanding deviations from the normal distribution were noted.

DISCUSSION

The relatively slight relationship between the condition of the individual endocrine glands and the fundamental personality of the individual possessing them has been emphasized by Curschmann[10] as follows: "In spite of

marked psychic sluggishness the premorbid psychic personality is always and even strongly preserved in severe myxedema." Furthermore, Engelbach [11] states: "One of the most common reactions attributable to the nervous system (in endocrine diseases) is that of general exhaustion and incapacity, which can be related to nearly all of the ductless glands." Finally forecasting the results of this endocrine study I [12] stated: "The study of the constitution will reveal the slight part played by the endocrine glands as such (with the exception of the thyroid) in the development and direction of the psychoses, and the dominant position of these glands in the ordering of bodily growth and form."

What may be said on the other side? Wertham [13] in a constitutional study of 923 cases of mental disease, found 21 per cent in whom disorders of growth were present in one form or another. The incidence was highest (36 per cent) among the schizophrenics, about equal in the paranoids and epileptoids (29 and 26 per cent) and lowest among the manic-depressives (2 per cent). Following these observations he states: "Just as patients with manic-depressive psychoses show a tendency toward unstunted and harmonious bodily growth . . . so they are also usually personalities with likewise harmonious mental maturation. The affective psychosis interrupts this mental development, but in most cases does not essentially deflect it. Schizophrenic patients, on the other hand, who show the largest number of disorders of physical growth, frequently show also in their prepsychotic mental development traits of inharmonious growth, immaturity and combinations of mental precocity and arrested development in intellectual, emotional and instinctive life."

Notkin [14] surveyed the population of a state hospital and found only eight cases of outright endocrinopathy among 6000 patients. "This infrequency seems to indicate that the relationship of the endocrine dysfunction to mental disorders has been overrated considerably, especially if we bear in mind the frequent occurrence of endocrine dysfunction without psychoses."

Experiments upon animals, and operations upon human beings serve to corroborate the conclusions to be drawn from the study of the material presented in this paper. Castration in either male or female does not alter the fundamental personality of the individual, turn him from a cycloid temperament to a schizoid one or vice versa. Nor does excision of the thyroid gland nor destruction of the hypophysis by disease. The patient with Addison's disease may present certain peculiarities of behavior that stamp him as different from his fellows, but given even as small a number as 20 patients with Addison's disease it is fairly certain that all the personality types enumerated above will be found among them.

The question of personality lies deeper in the mists of genetic constitution than in the endocrine system.

Two important functions, as far as the personality is concerned, may safely be granted to the endocrine system. These are emotional stability,

and energy drive. The irritability and emotional instability seen in hyperthyroidism, in hyperinsulinism, in hypoparathyroidism and in certain other endocrinopathies, are relieved by restoring the normal endocrine balance. The energy drive is augmented to a greater or less degree by correcting any deficiency of the hypophysis, thyroid, suprarenals or gonads. Nevertheless, as far as determining whether an individual shall be a proud, sensitive, suspicious, paranoid individual or a timid, shut-in dreamy schizoid person; a boisterous, jolly, hail-fellow-well-met cycloid, or a moody, pedantic, egocentric epileptoid individual, the endocrine glands would seem to have little say in the matter.

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THE RELATIONSHIP OF THE FLAT CHEST TO INTELLIGENCE *

By S. A. Weisman, M.D., F.A.C.P., *Minneapolis, Minnesota*

In a series of reports [1] previously published I emphasized the following facts:

1. That the healthy normal adult chest was, contrary to the general belief, flat and that the tuberculous chest was deep.
2. That at birth the chest is almost round, and that by the age of five about 87 per cent of the total flattening out process already has taken place, and that there is only about 13 per cent difference between the contour of the chest of a five year old child and a fully mature adult type of chest, which is attained at puberty.
3. That children from better environmental districts are not only taller and heavier but also have a flatter type of chest.

It is the purpose of this study to determine whether or not there is any correlation between the shape of the chest and intelligence.

In 1893, Porter,[2] from a study made on many thousands of St. Louis school children concluded, " Children who possess more than ordinary power of mental labor, as measured by their progress in their studies, are heavier, taller and larger in girth of chest than their less gifted companions of the same age."

About thirty years ago Rietz's [3] measurements of the height and weight of some 20,000 Berlin school children showed that brighter children are better developed physically.

Goddard's [4] measurements of the height and weight of feeble minded children indicated that there is a close correlation between physical growth and mental activity, and in 1917 Courtis [5] believed that children who are poorly developed physically are usually dull mentally.

Francis Galton,[6] in his book " Hereditary Genius," published in 1869, concluded that men of genius tend to be well developed physically. He states, " A collection of living magnates in various branches of intellectual achievement is always a feast to my eyes: being, as they are, such massive, vigorous, capable-looking animals."

In 1918 Gowin [7] made a study of the height and weight of 1,037 American executives, which number included governors, United States senators, mayors of leading cities, University presidents, bishops, merchants, manufacturers, insurance company presidents, and railroad company presidents. He found the average height to be 71.4 inches and the average weight 181.1 pounds (table 1). The average height of 1,000,000 United States army recruits is 67.5 inches.

* Read at the Philadelphia meeting of the American College of Physicians, May 1, 1935.
From the Department of Medicine, University of Minnesota and Glen Lake Sanatorium, Oak Terrace, Minnesota.

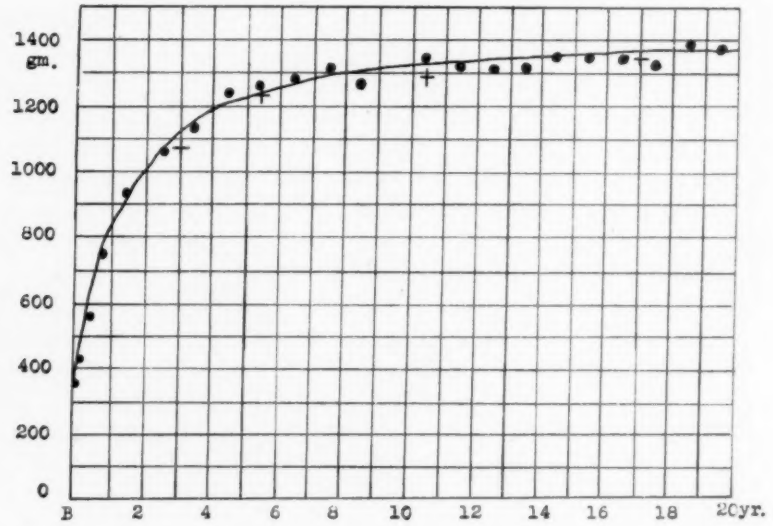
TABLE I

Physique in Relation to Position
(Gowin)

Class	Height	Difference	Weight	Difference
Bishops	5 : 10.6		176.4	
Preachers, Small Towns	5 : 8.8	1.8 in.	159.4	17.0 lb.
University Presidents	5 : 10.8		181.6	
Presidents, Small Colleges	5 : 9.6	1.2 in.	164.0	17.6 lb.
City School Superintendents	5 : 10.4		178.6	
Principals, Small Towns	5 : 9.7	.7 in.	157.6	21.0 lb.
Presidents, State Bar	5 : 10.5		171.5	
County Attorneys	5 : 10.0	.5 in.	162.4	9.1 lb.
Sales Managers	5 : 10.1		182.8	
Salesmen	5 : 9.1	1.1 in.	157.0	25.8 lb.
Railroad Presidents	5 : 10.9		186.3	
Station Agents	5 : 9.4	1.5 in.	154.0	31.7 lb.

Woodrow [8] in 1919 and Baldwin and Stecher [9] in 1922 showed that there is an intimate relationship between mental and physical development.

In the development of the brain Scammon [10] has shown that the greatest percentage of growth takes place in the first year of life and that by the age of five the brain has attained to about 85 per cent of its total adult weight (graph 1). This development of brain weight runs practically parallel with the flattening out process of the chest from infancy to maturity.



GRAPH 1. Observed and calculated weight of the total brain (both sexes)—from birth to twenty years (Scammon).

TABLE II

Relationship of Scholastic Standing to Thoracic Index—Girls

Age	Grade	No. Cases	Av. T. I.	Av. Dev.	St. Dev.	P. E.
5	F	35	721	3.8	4.01	.4586
	A	29	725	3.6	4.22	.5261
	C	199	714	3.4	4.70	.1488
6	F	129	710	3.4	4.27	.2495
	A	106	706	3.2	4.44	.2900
	C	444	713	3.1	4.12	.1281
7	F	111	705	3.4	3.05	.1888
	A	90	706	3.6	4.46	.3102
	C	475	723	3.8	4.68	.1484
8	F	111	717	3.4	4.09	.2563
	A	127	708	2.9	3.84	.2225
	C	595	709	3.2	4.23	.1147
9	F	127	704	3.7	4.17	.2495
	A	77	703	3.8	4.82	.3710
	C	671	702	3.2	4.30	.1147
10	F	131	699	1.9	4.19	.2361
	A	84	698	3.2	3.90	.2832
	C	610	695	3.6	4.60	.1281
11	F	139	701	3.5	4.22	.2361
	A	65	684	4.2	5.39	.4519
	C	371	676	2.8	4.25	.1416
12	F	111	707	3.8	4.83	.2833
	A	30	686	3.1	3.97	.4845
	C	537	696	3.9	4.82	.1349
13	F	57	695	4	5.20	.4656
	A	45	698	4.5	6.11	.6137
	C	331	690	4.3	5.31	.2225
14	F	62	702	4.2	5.70	.4858
	A	44	688	3.6	4.70	.4719
	C	308	683	4.5	5.43	.2090
15	F	74	690	4.2	5.32	.4114
	A	18	652	2.3	2.69	.4384
	C	358	681	4.2	5.48	.2023
16	F	41	706	5.6	6.70	.6745
	A	11	679	5.5	8.53	.1754
	C	208	679	4.2	4.95	.2292
17	F	27	682	4.3	5.19	.6699
	A	7	675	4.0	4.66	1.214
	C	83	677	4.5	5.03	.3709
18	F	7	733	3.1	4.18	1.079
	A	2	654	2	2.24	1.011
	C	17	691	5	5.99	.9438

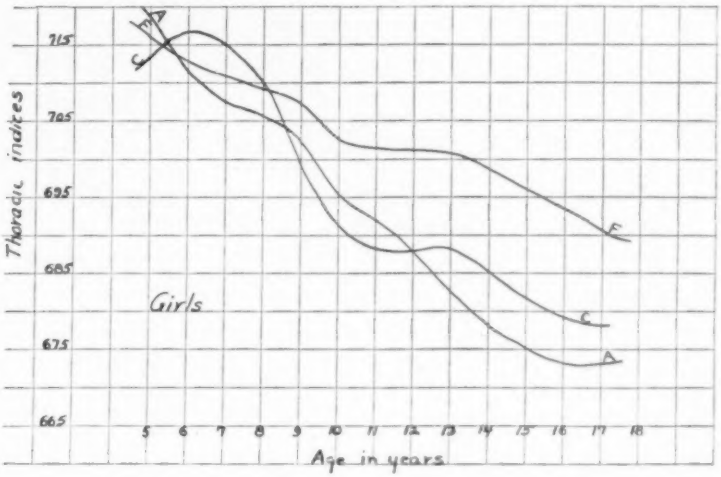
TABLE III

Relationship of Scholastic Standing to Thoracic Index—Boys

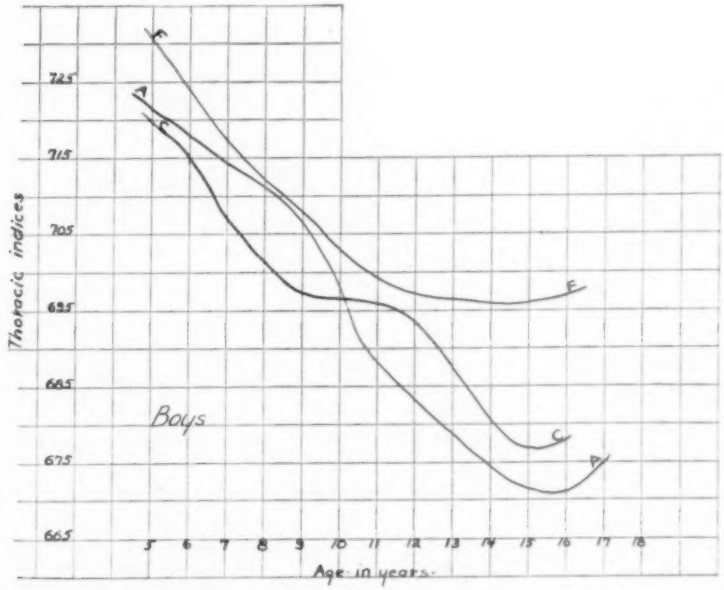
Age	Grade	No. Cases	Av. T. I.	Av. Dev.	St. Dev.	P. E.
	F	37	735	3	3.5	.3794
5	A	21	728	4.2	5.1	.7486
	C	186	724	3.5	4.4	.2158
	F	175	724	3.6	5.1	.261
6	A	67	710	4	5	.404
	C	473	712	3.4	4.2	.128
	F	225	715	3.3	2.4	.1074
7	A	49	712	3.1	4.1	.3913
	C	438	710	3.2	4	.1281
	F	275	713	3.3	4.24	.1753
8	A	68	715	3	3.6	.2986
	C	593	702	3.1	3.6	.0944
	F	214	709	3.5	4.3	.202
9	A	47	717	3.8	4.6	.45
	C	605	697	3.2	4.29	.1146
	F	234	704	3.3	4.42	.1966
10	A	50	692	3.2	4.08	.3842
	C	677	693	3.2	4	.1011
	F	209	696	3.3	4.22	.1956
11	A	42	686	3.5	4.6	.4113
	C	570	699	3.7	4.6	.0539
	F	164	696	3.2	4.6	.2495
12	A	23	683	4	5.25	.5193
	C	417	698	3.6	4.43	.1417
	F	158	699	4.1	5.23	.2757
13	A	25	689	4	6.1	.8094
	C	226	689	3.8	4.5	.2023
	F	101	691	4.6	3.5	.2293
14	A	13	673	2.1	3.1	.5598
	C	291	679	3.9	3.8	.2225
	F	170	702	4.5	5.48	.2842
15	A	17	666	2.2	4.4	.6745
	C	297	675	4.3	5.4	.2090
	F	137	694	4.2	5.1	.3102
16	A	9	665	2.5	2.9	.6745
	C	237	671	4.2	5.49	.2428
	F	53	691	5.4	6.7	.6070
17	A	6	684	5	5.7	1.551
	C	110	687	4.4	5.4	.3439
	F	10	718	5.2	6.1	1.281
18	A	2	669	2	1.4	.9510
	C	28	685	5.4	4.9	.5600

Therefore, the deduction occurred to me: if, as shown by the aforementioned investigators, taller and heavier individuals tend to be more intelligent; and, as shown by my previous studies, taller and heavier children have the flatter, more healthy type of chest, then there should be a correlation between the flat chest and intelligence.

The present study was made on 14,844 Minneapolis school children, from



GRAPH 2. Relationship of thoracic index to scholastic standings. These curves represent the average thoracic indices with one application of the three point rule.



GRAPH 3. Relationship of thoracic index to scholastic standings. These curves represent the average thoracic indices with one application of the three point rule.

the ages of five to seventeen. This number consisted of 7,740 boys and 7,104 girls. The school grades, as given by the teachers, were considered a measure of the child's intelligence. The grades were divided into three groups. The "A" students were put into the class "A" group; the "B" and "C" students were put into the class "C" group; and those below, including the subnormals, were put into the "F" group.

The average thoracic index was then determined for each group according to age (tables 2 and 3, graphs 2 and 3). The thoracic index is the ratio of the depth of the chest to the width, taken against the skin at the nipple line.

The findings indicate that the "F" group have, on the average, a deeper chest, that is, a higher thoracic index than the "A" and "C" groups. This difference seems to be much more marked just before the age of nine in the girls and perhaps a little later in the boys. From there the difference between the "A" group and the "F" group becomes markedly greater. The "C" group seems to fall in between the "A" and the "F" groups after the age of 12 in the girls and between the ages of 10 and 11 for the boys. Before these ages the "C" boys seem to have the flattest type of chest, and the girls' "C" group is flatter than the "A" group between the ages of nine and almost twelve. After age 12 in the girls and ten and one-half in the boys the "A" group, both in the boys and in the girls, shows a definitely flatter type of chest, or one with a lower thoracic index.

Conclusions

1. The flat-chested children are taller and heavier than the deep-chested children.

2. There appears to be a definite correlation between the shape of the chest and intelligence in children.

3. The flat chested children have, on the average, better school grades.

4. Therefore, it is evident that the flat chested children are, on the average, taller, heavier, and display a higher degree of intelligence.

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ACUTE LYMPHATIC LEUKEMIA IN A CHILD OF FOUR YEARS WITH A SEVERE GRANULOPENIC PHASE PRECEDING A REMISSION *

By Lewis B. Flinn, M.D., F.A.C.P., *Wilmington, Delaware*

The study of blood dyscrasias has led to their division into a large number of groups, diseases and syndromes with a baffling nomenclature. The etiology of very few of these various subdivisions is proved and on this account there is no detailed classification which is generally acceptable. Ultimately perhaps a more definite etiological classification will be possible. The work of Castle [1] and his associates on the etiology of the macrocytic anemias has done much to clarify the confusion which existed in this field.

Search for the etiological agent in the leukemia group has so far met with less success. Here there is even more overlapping and confusion. Neither the infectious nor the neoplastic theory of the causation of the leukemias is entirely convincing, although the acute leukemias rather suggest infection and the chronic type, tumor. Possibly the etiology ultimately may be attributed to some factor, or imbalance of several factors, now unknown but similar in principle perhaps to those discovered to be operative in macrocytic anemias. Gottlieb [2] for instance believes that the reticulo-endothelial system exerts an inhibiting influence upon the granulopoietic system and suggests the possibility that in certain states where granulopenia exists the normal balance between the two systems is upset. In the case he reported where the erythrocytes, granulocytes and hemoglobin were all greatly lowered, splenectomy was performed with the idea of relieving the reticulo-endothelial inhibition. The blood promptly returned to practically normal for a period; then, perhaps because the rest of the reticulo-endothelial system took up the splenic function and because of the additional strain of an acute infection, the anemia greatly increased and death occurred.

The protean nature of leukemia is well known. Jackson [3] has emphasized the many and varied forms of malignant lymphoma. More recently since the number of cases of agranulocytosis has increased, the differentiation of this condition from acute leukemia has occasionally given rise to diagnostic difficulties. Schultz [4] in 1922 first presented agranulocytosis as a distinct clinical entity, perhaps a distinct disease. When one considers only such cases as he first described, those which are characterized by prostration, fever, necrosing stomatitis or pharyngitis, marked leukopenia, extreme decrease or absence of polymorphonuclear neutrophiles, very little anemia and usually no platelet change—the clinical picture certainly suggests a distinct disease. Doan [5] has described very thoroughly the various phases of this condition. Occasionally a rather similar clinical picture occurs fol-

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lowing known sepsis; also many cases have an insidious onset and the few which recover from the initial attack frequently have a recurrence of the disease. The author at the present time has under observation a case of two years' standing in which the initial attack occurred after small doses of radium for menorrhagia. Subsequent leukopenia in this case seemed to have a definite relation to the menstrual cycle and with reëstablishment of the menses the blood count has remained normal. The precipitating factor in this syndrome of granulopenia, therefore, may vary greatly.

Several recent reports in the literature seem to point toward some actual connection between agranulocytosis and leukemia. Burkens [6] reported a case with a leukopenia of 2,000 cells, all lymphocytic, which came on in conjunction with an infection of a foot. After the abscess was opened the blood picture returned to normal. One year later there occurred lymph node enlargement as well as enlargement of the liver and spleen. The white count showed mostly lymphocytes. No autopsy was reported. Easton [7] reported a case of agranulocytosis which curiously enough preceded acute myelogenic leukemia. Potter [8] and others reported similar cases. Rosenthal [9] in discussing the various diseases exhibiting marked leukopenia cited no case, even with temporary recovery, in which there was such a severe leukopenia, neutropenia and thrombocytopenia as in the present case report. M. M. Strumia [10] reported three cases of leukemia with a granulopenic phase. Two were granulocytic leukemias. The third simulates the case reported here except that the leukopenia was not so great and the child not so ill clinically; and at the onset in Strumia's case there was a definite infection in the form of an acute pericarditis with effusion, whereas in the author's case no infection could be demonstrated when the patient was first seen. Givan and Shapiro [11] reviewed 30 reported cases of agranulocytosis in childhood. Only four recovered; one of those, an infant of three months, had pyodermia, another had a recurrence every three weeks for 20 years, another had an acute upper respiratory infection just preceding the agranulocytosis. None of these had a leukopenia under 4,800. The fourth case to recover had a leukopenia of 600 and no granulocytes but had four months of purulent otitis media as an antecedent. Seventeen of the remaining 26 fatal cases apparently had no sepsis or demonstrable acute infection at the onset. From the data given these cases could not be differentiated from aleukemic leukemia or from a granulopenic phase of leukemia such as is reported in the case in this paper. Platelets when reported were diminished. Perhaps had these cases recovered from this granulopenic stage a definite leukemic picture would have followed.

Case Report

Summary of History. The patient was a white girl, four years old. The mother's only other pregnancy had resulted in a previous miscarriage. The Wassermann tests on both mother and child were negative. The child had always been well except for pertussis and measles. The present illness was of gradual onset over

a period of three or four weeks with increasing weakness, lack of appetite, and slight irregular fever.

Physical Examination, November 18, 1932. The patient was pale and did not look well. Temperature 102° F. Neither the ears, mouth, teeth nor pharynx appeared unusual. There was a slight discharge from both nostrils. The mouth, teeth and pharynx showed nothing abnormal. The tonsils were only slightly enlarged. There were numerous enlarged cervical lymph nodes; epitrochlear and axillary nodes were palpable; inguinals not definitely enlarged. The thyroid was not enlarged.

The lungs were clear throughout. The relative cardiac dullness extended 5.5 cm. to the left in the fifth interspace; 2.5 cm. to the right in the third interspace. Transverse diameter of the heart was 8 cm. Just inside the apex there was a blowing systolic murmur, not well heard in the axilla or at the pulmonic area. The second sound was accentuated. The spleen was definitely palpable about 2 cm. below the costal border. The liver was not definitely felt. The abdomen and the extremities were otherwise negative.

The blood picture was as follows: Hgb. 32 per cent (Dare). Red blood cells, 2,000,000. White blood cells, 11,200. Polymorphonuclear leukocytes, 20 per cent. Small lymphocytes, 64 per cent. Large lymphocytes, 12 per cent. Myelocytes, 4 per cent. There was moderate anisocytosis and slight poikilocytosis. The platelets were reduced in number.

First Hospital Admission, November 20 to 23, 1932. Laboratory data: The coagulation time was three and a half minutes. The bleeding time was four minutes. The Van den Bergh test was negative. Fragility test: hemolysis began in 0.42 per cent sodium chloride solution and was complete in 0.32 per cent. The blood picture was essentially the same as given above.

A transfusion of 200 c.c. of citrated whole blood was given the day after admission. At this time the temperature was 104.4° F. and there was marked swelling of the posterior cervical lymph nodes on both sides. The temperature after ranging from 102° to 103° for two days dropped to 99° on the third day, coincident with a typical German measles eruption and prompt subsidence of the swelling of the post-cervical lymph nodes. During this episode the white count fell to 3,600 cells with only 5 per cent polymorphonuclear leukocytes. The patient was removed from the hospital and for two days had no fever. A necrotic ulcer then developed in the upper pole of the left tonsil, the temperature rose to 102°, the child became critically ill and returned to the hospital December 2, where she stayed until January 23, 1933.

The white blood cells numbered 10,140, with 12 per cent polymorphonuclear leukocytes. A blood transfusion of 200 c.c. was given immediately. Two days later the prostration had increased, the ulcer was becoming larger and deeper, the temperature ranged from 104° to 105° and the white cell count dropped to 3000 with 6 per cent polymorphonuclear leukocytes. A transfusion of 200 c.c. of blood was again given. The white cells dropped to 2650 and then to 1300. The red cells dropped to 1,500,000 without marked change in size or shape. The platelet count was 10,500.

At this time 0.7 gm. of pentnucleotide was given twice daily, once intravenously and once intramuscularly. Necrosis began at the left corner of the lower lip. After nine days of pentnucleotide therapy the white cells dropped to 700 with 9 per cent polymorphonuclear leukocytes. The small lymphocytes, the predominant cells, were immature with unusually large nuclei. Chart 1 shows the detailed blood studies as well as the essential clinical findings and therapeutic measures. At this time bilateral otitis media and bronchitis developed. The child was so critically ill that no hope was given for her recovery. Finally the white cells began to rise gradually from 700 on the twelfth day of pentnucleotide therapy to 2000 on the sixteenth day, December 21. The reticulocytes rose to 3 per cent on December 20. The temperature which had ranged between 102° and 105° gradually came down to 100° (rectal) on the

CHART 1. The upper section of chart shows detailed blood studies during the most critical month of patient's illness, during the second hospital admission. The middle portion indicates temperature range and main clinical features. The lower portion gives the important therapeutic measures which were used.

Date—Dec.	2	4	6	7	10	12	14	15	16	17	18	20	21	22	24	26	28	30	31
Hgb. % (Dare)	35		32	28	30	35	30				55	60	59	60	60	64	74		74
R.B.C.	2.0		1.7	1.5	2.2	2.4	1.7			2.1	2.8	3.8	3.2	3.5	2.9	3.8	3.9		4.1
W.B.C.	10,140	3,000	2,650	1,300	1,250	1,750	700	700	750	1,200	1,100	1,650	2,000	2,900	2,900	3,900	5,800	6,700	11,800
P.M.N.	12	6	5	9	12		9			44	18	24	45	40	38	45	49	71	71
S.L.	85	94	95	91	88		90			10	59	59	49	49	56	40	25	21	27
L.L.	2									12	4	9				2	4	3	2
Juvenile P.M.N.							1				6	3	2	5	2	5	9		
Unclassified										38	13	5	4	6	4	8	11		
Platelets			10,500	16,170															240,000
Reticulocytes			0.2%	0.2%	0.26%	0.2%	.03%								0.2%				
Rectal a.m. Temp. Fahr. p.m.	103 104.4	104.5 105	104.4 105.6	102 104	104 104.5	103 104.5	103 105	103.2 104.4	103.4 104.6	102.6 104.2	101 104.2	101 103	100.4 101.2	100 101	98.8 100.8	99 99	99.8 99	99.6 99.8	99 99.8
Clinical Features			Necrosis lower lip			Bronchitis	Bilat. otitis media				Clinically much improved		Coughed out left tonsil			Pharynx healed	Abscess right arm		Still stronger
Pentnucleotide	1.4 grams daily									0.7 gram daily									
Transfusions Blood in c.c.	200	200	250				170	180		250	140	90			240				
Liver Extract #343	2 c.c.	2 c.c.	3 c.c.																

twenty-first day and on that day she coughed out her sloughed left tonsil. The hemoglobin and red cells had increased to 59 per cent and 3,200,000 respectively. The tenth transfusion was performed on December 24. On the twenty-fifth the pharynx was completely healed and the subsequent improvement seemed truly miraculous. In a few days she was sitting up, had a ravenous appetite and on discharge, January 23, 1933, was able to walk alone. The entire blood picture including the platelet count had returned to normal.

Comment

The diagnosis of German measles rather than a toxic eruption seemed justified because of the sudden exacerbation of fever lasting three days, coincident with enlargement of post-cervical lymph nodes, pharyngeal injection, appearance of a typical eruption on the third day as the fever subsided, followed by prompt subsidence of the lymph node swelling. There was also a transient leukopenia at this time.

The necrotic ulcer of the left tonsil started during this attack of rubella. On the seventeenth day of observation during the second hospital admission the fever increased; leukopenia became more pronounced and the child became so desperately ill that no one who saw her from the twenty-second day to the thirty-second day expected her to recover. It is interesting to note that blood transfusions had apparently no good effect upon the granulopenia until the leukocytes began to increase 12 days after pentnucleotide therapy was started. The latter was given both intramuscularly and intravenously. When improvement did set in, the hemoglobin and erythrocytes increased more rapidly than could be explained by transfusions alone. Our observation of this case and findings in several other cases of agranulocytosis is in accordance with Jackson's [12, 13] impression that if blood transfusions have any effect on the leukopenia in these cases they increase it. Doan [5] suggests that there may be a temporary decrease in the leukocyte count followed by a rise due to nucleotide set free by destruction of the transfused cells. Reznikoff [14] takes a similar view in discussing nucleotide therapy in these cases. It is our policy then to transfuse not on account of the leukopenia but solely to relieve anemia.

Interim Progress: January 2, 1933 to May 15, 1933. For three months the patient was exceptionally well at home and according to the mother, more active and stronger than ever before. There was a gain of about five pounds in weight. The left ear, however, continued to discharge. Blood counts during this period were as follows:

	Hgb. (per cent)	R.B.C. (millions)	W.B.C.	P.M.N. (per cent)
2/13/33	71	4.1	11,600	53
3/1/33	78	4.2	10,200	54
3/14/33	80	4.2	11,200	42

On March 15, 1933 some swelling was noted about the joints and small bones of the hands and the child complained of bone pains in the wrists, phalanges and femora. Irregular fever was again found present.

On April 30, 1933 an acute follicular tonsillitis developed. The stub of the previously sloughed out left tonsil became slightly enlarged. Temperature ran between 102° and 104° F. for three days. Blood counts at about this period were as follows:

	W. B. C.	P. M. N.
4/28/33	18,000	30
5/6/33	18,000	20
5/11/33	65,000	3

The bone and joint pains and irregular fever continued, and on May 15 the patient was readmitted to the hospital.

Third Hospital Admission: May 15 to July 15, 1933. During this final hospital admission the clinical course of the illness was marked by irregular fever between 99 and 105° F. There was some swelling during the first three days of the cervical and axillary lymph nodes but after this time no lymph gland enlargement was ever made out. The spleen was at no time in this period palpable.

The fusiform swelling of the phalanges, and particularly of the proximal phalanx of the second digit on each hand, gradually increased. Roentgenograms at various times showed thinning of the cortical zone and rarefaction in the bones of the hands, the radius, ulna and femora. (See figures 1 and 2.)

Swelling developed in the region of the left mastoid and on June 2 mastoidectomy was performed under gas anesthesia. A variety of organisms was recovered from the mastoid cells; a blood culture at this time remained negative. Recovery from the operation was uneventful.

A vesicular eruption simulating herpes zoster appeared over the left thigh and flank; it cleared up within a week. This finding is interesting in the light of a report of Craver and Haagensen [15] who found seven cases of herpes zoster in 329 cases of Hodgkin's disease, lymphosarcoma and leukemia. They call attention to the fact that such an incidence is considerably greater than that found in any general hospital.

The general trend of the illness was downward. Fever continued though the lungs remained clear and there was at no time any evidence of endocarditis. In the last two or three days of life a large rapidly advancing necrotic lesion developed in the pharynx and also a second similar lesion about the anus. Death occurred on July 15, on the two hundred forty-first day of observation.

Laboratory Studies. The red blood cell count fell from 4.7 million to 1.7 million the day before the patient's death. The hemoglobin likewise fell from 82 to 34 per cent. The white blood cell count was taken daily and showed marked variations which were not explicable by the apparent clinical condition. The total w.b.c. count usually varied between 9,000 and 56,000. Two days before death, however, it was 32,700 and on the day preceding death it had fallen to 1,600. The differential counts showed that the lymphocytes constituted between 92 and 100 per cent of the total white cells; most of the lymphocytes were immature. The polymorphonuclear leukocytes ranged from none to 8 per cent of the total.

Platelet counts revealed a total absence of platelets; none were ever found. The reticulocyte count was always below normal. This was in contrast to the first admission. The coagulation time was not increased. The tourniquet test would occasionally cause petechial hemorrhage. The fragility test was not markedly changed; hemolysis began at 0.38 per cent and was completed at 0.32 per cent.

The results of therapy, given without expectation of cure but in the hope of at least temporary improvement, were disappointing. Seven transfusions were carried out in this admission, making a total of 17 in all. For 26 days pentnucleotide was administered in doses of 0.7 gm. to 1.4 gm. daily. Reactions to pentnucleotide were at times marked, characterized by vomiting with the appearance of mild general

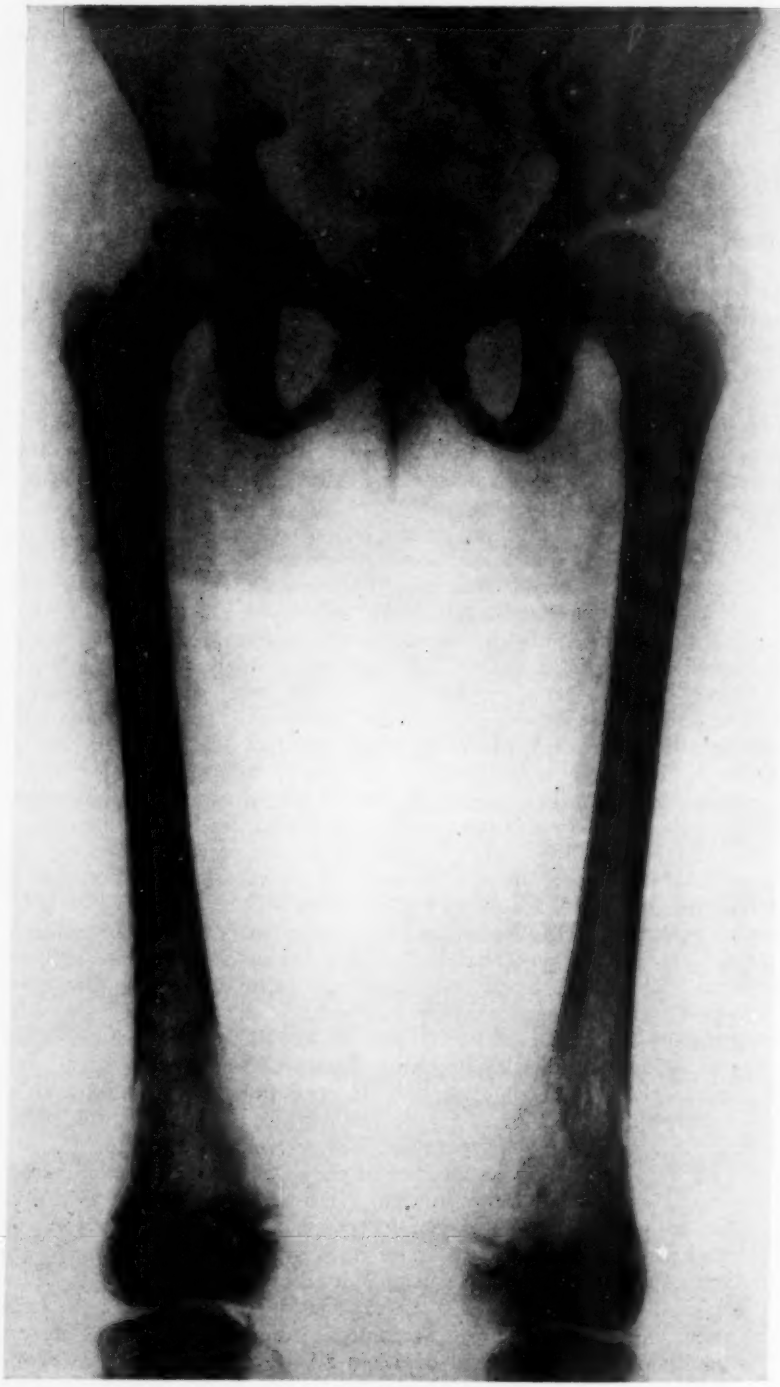

FIG. 1. Roentgen-ray demonstrates marked rarefaction of bones, particularly marked in the lower end of both femora. At autopsy the cortex of the rarefied area in the left femur was of egg shell thinness.

shock. Several abscesses developed at the site of intramuscular injections and when opened the purulent exudate on smear showed polymorphonuclear leukocytes and staphylococci. Following the pentnucleotide two series of daily injections (one of four and one of seven days) of leukocytic cream were given. The dosage was 8 c.c. No clinical or hematological effect was noted.

Beginning on July 6, Addisin was given in 10 c.c. doses three days apart. It had been suggested by Morris [16] and his coworkers that this material was of advantage in agranulocytic angina and was under trial in leukemia. In the present case it produced no demonstrable effect.

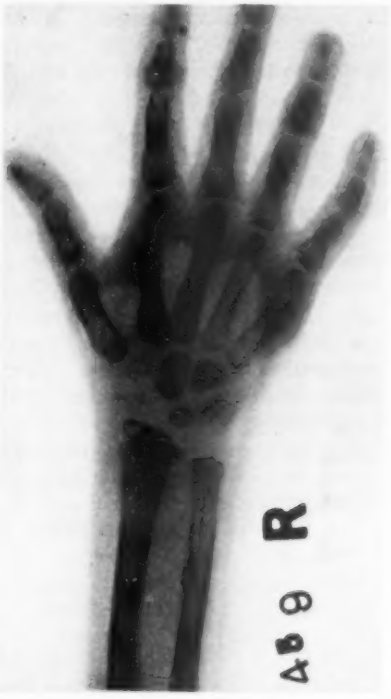

FIG. 2. Roentgen-ray demonstrates rarefaction of both radius and ulna and of small bones of the hand.

AUTOPSY REPORT

Douglas M. Gay, M.D., Pathologist, Delaware Hospital

The body is that of a fairly well developed and slightly emaciated white female child 103 cm. in length. Rigor mortis is present in the jaw only. Dependent parts are livid. The eyes, ears and nose are normal. The pupils are round, regular and equal, each measuring 0.4 cm. in diameter. A superficial ulcer about 0.5 cm. in diameter is present on the left side of the dorsum of the tongue. Other small superficial ulcers are present on the palate. The pharynx and right tonsillar region are necrotic and appear to be covered with a soft light brown material. An irregular opening extends through the skin over the left mastoid region into the bone and is filled with a foul smelling brown material. A longitudinal incision 2 cm. long is present on the outer aspect of the right thigh. This extends into the subcutaneous tissue and is filled with a small gauze. The anus and surrounding tissue are dark red brown in color and present several bullae filled with light brown fluid.

Peritoneal Cavity: Surfaces smooth and glistening. No adhesions or free fluid present. Mesenteric lymph nodes are soft, red, and moderately enlarged. The largest of these measures about 1 cm. in diameter. *Pleural Cavities:* Surfaces smooth and glistening. No adhesions or free fluid present. *Pericardial Cavity:* Surfaces smooth and glistening. No adhesions or excess of fluid present.

Heart: Normal in size, shape and position. Epicardium is smooth and transparent. Myocardium homogeneous, dull red and firm in consistence. Endocardium is thin and transparent. Cavities, valves and coronaries are grossly normal. *Lungs:* Normal in shape and size. Soft and crepitant throughout. Multiple sections reveal normal pale pink lung tissue. Tracheo-bronchial lymph nodes are not enlarged. *Spleen:* Weight 174 grams. Moderately enlarged. Normal in shape and firm in consistence. The capsule is thin over a smooth dark purple surface. On section the spleen is a similar dark purple color and markings are not readily made out. A small amount of pulp scrapes away. *Pancreas:* Normal in size, shape, color and consistence. *Liver:* Weight 1250 grams. Moderately enlarged. The edges are rounded, capsule is thin over a smooth red brown surface. On section the liver is a similar red brown color and the markings are not distinct. The enlarged size of the liver is apparently due to an increase in substance rather than congestion. The gall-bladder is not remarkable. *Gastrointestinal Tract:* Grossly normal throughout. Peyer's patches are not prominent. *Adrenals:* Normal in size and shape. Medullary portion is very thin. Cortical portion is light yellow brown in color. *Urinary Organs:* The kidneys are about twice normal size. The capsule strips spontaneously from a dark red surface. On section the cortex measures 0.6 cm. in average thickness and is dark red in color. The medullary portion is pale red gray. The calices, pelves, ureters and bladder are normal. *Genital Organs:* Grossly normal. *Aorta:* Normal. *Lymph Nodes:* Superficial lymph nodes are slightly enlarged, only in the left cervical region. Mesenteric nodes are slightly enlarged, soft and red. The retro-peritoneal lymph nodes in the lumbar region are moderately enlarged, the largest being 2 cm. in diameter. This group of nodes presents a mass of nodules which are firm and pale gray in color. A series of dark red nodes extends along the posterior portion of the rectum. These average 0.5 cm. in diameter and are soft in consistence. The tracheo-bronchial lymph nodes are not enlarged. *Bones:* The ribs are brittle and the bone marrow is pale gray red in color and the sternal marrow is also pale red gray. The lower end of the left femur is minutely roughened and the periosteum appears to be elevated a distance not greater than 0.1 cm. by a soft red gray infiltration. The cortex of this portion of the femur is very thin and the marrow cavity is large. The vertebral marrow is yellow in color, fatty in consistence and contains numerous small hemorrhages. Other bones are not investigated.

Microscopic Notes. Heart: The myocardium is not remarkable. A thin layer of cells is infiltrating beneath the pericardium. These cells are of medium size, round in shape and resemble the tumor cells described below. *Lung:* Normal. *Spleen:* Numerous large mononuclear cells containing orange brown granules (hemosiderin) are distributed throughout. There are also numerous large phagocytic cells containing cellular débris. As far as can be made out the phagocytized material consists of nuclear and cytoplastic remnants. Masses of tumor cells are distributed around the small arteries and trabeculae. The detailed description of these cells is given under lymph nodes. A few foci also contain cells resembling eosinophilic myelocytes. *Pancreas:* An infiltration of tumor cells is present in the stroma around the larger blood vessels. Otherwise the organ is normal. *Liver:* Small masses of tumor cells are present in every portal space. The liver cells are faint staining, the cytoplasm is granular and the nuclei are sharply outlined but apparently deficient in chromatin. *Adrenal:* Groups of tumor cells are present in the medullary portion and around some of the blood vessels in the capsule. *Kidney:* The cortex appears to be

greatly thickened by the presence of tumor cells and diffuse hemorrhage. The perivascular distribution of tumor cells noted in the other organs is especially prominent in the kidney. The tubules appear to be surrounded by masses of hemorrhage and the glomeruli by masses of tumor. There is no evidence of tumor within the glomerular capsule. The medullary portion of the kidney is not remarkable. Perivascular groups of tumor cells are present in the loose connective tissue near the papillae. *Aorta:* Normal. *Intestine:* The one section studied is not remarkable. *Lymph Nodes:* Sections of four lymph nodes from various parts of the body show a similar picture varying in degree. Only a slight suggestion of the follicular structure of the node is present. The sinuses, however, are easily made out. These contain numerous large mononuclear cells and many smaller cells interpreted as tumor. The picture is not characteristic of lymphoblastoma, in that the follicles may occasionally be discerned. The sinuses are not packed with the tumor cells and the cells themselves are not of the usual appearance. The average tumor cell is about 14 microns in diameter. It is round with dark red cytoplasm. The nucleus is round and contains a moderate amount of chromatin. Mitotic figures are seldom found. The large phagocytic cells described elsewhere are also present in the lymph nodes. The general appearance of these cells is similar to the tumor cells, although the former are larger and the cytoplasm tends to be brighter red. The phagocytized material consists of cellular débris and red blood corpuscles. A few cells resembling normoblasts and others resembling myelocytes are present in the sinuses. There appears also to be a small amount of blood in the sinuses of some of the nodes. A few tumor cells are apparently present in the capsule. *Bone:* A section of the femur shows a heavy infiltration of tumor cells between the bone and the periosteum. The tumor cells also extend above the periosteum among fibers of striated muscle. The bone marrow shows a diffuse infiltration with tumor cells although an abundance of fat tissue remains. There is very little evidence of hematopoiesis, although an occasional polymorphonuclear leukocyte is present. There are numerous small hemorrhages. The picture is essentially the same in the marrow from the sternum, ribs, femur and vertebrae.

Discussion

The clinical picture and blood studies when the patient was first seen suggested the possibility of a leukemia or a severe secondary anemia, possibly due to some previous infection. None of the usual physical signs of leukemia presented themselves, however, and except for the high percentage of small lymphocytes the whole picture in the second week could be explained on the basis of a secondary anemia. The attack of German measles was the precipitating factor in the onslaught of the severe, almost fatal episode of agranulocytosis. Apparently this was relieved by nucleotide therapy with supporting blood transfusions. Differentiation between an aplastic anemia and malignant neutropenia was difficult for a time. It is interesting that when the blood picture returned to normal the platelets did also. The two months of almost perfect health following the second hospital admission must be considered in the light of later developments, as merely a remission of leukemia. It is difficult, however, to consider the leukopenic episode as entirely leukemia unless primary agranulocytic angina shall be found to be merely one form or phase of leukemia. Certainly they both may have remissions but certainly too, leukemia with leukopenia rarely if ever reaches

the extreme cited in this case without at once ending fatally. During the last admission, even up to 48 hours before death the child never appeared as ill clinically as in the previous leukopenic state. It is interesting to note that the first phase of the disease was preceded by an attack of rubella, a disease usually associated with leukopenia, and that the onset of the hyperleukocytic leukemia phase was coincident with an attack of follicular tonsillitis, a disease usually associated with leukocytosis.

Summary

I. The protean nature of leukemia is briefly discussed particularly in regard to its possible relationship with primary agranulocytic angina.

II. An unusual case of acute lymphatic leukemia of 8 months' duration in a child of four years is reported in detail, the salient features of which are:

(*a*) An extreme agranulocytic phase followed by a remission of two months.

(*b*) A typical terminal leukemic phase without demonstrable lymph node enlargement except at autopsy.

(*c*) Marked leukemic bone changes, clinically, by roentgen-ray and at autopsy.

(*d*) Herpes-zoster.

(*e*) The leukopenic phase was apparently precipitated by an attack of rubella, a disease usually associated with leukopenia, and the final leukocytic or leukemic phase was apparently precipitated by an attack of acute follicular tonsillitis, a disease usually associated with leukocytosis.

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CASE REPORTS

AN INSTANCE OF POSSIBLE CIRRHOSIS OF THE LIVER INDUCED BY A HAIR TONIC CONTAINING CARBON TETRACHLORIDE *

By B. B. Vincent Lyon, M.D., D.Sc., F.A.C.P., *Philadelphia, Pennsylvania*

There are many substances now known to produce definite hepatic injury, such as chloroform, various arsenicals, various members of the quinoline series such as cinchophen, etc. As a result of numerous publications regarding their danger the medical profession has learned to exercise greater caution in their use.

Because of the increasing popularity of its use as a cleaning fluid by the general public, carbon tetrachloride (and trade marked cleaning agents containing it) should also be included in this group. Indeed, in current interest, it now leads the list of chemicals which can produce liver injury.

For many years it has been considered an industrial hazard. There is no doubt that the large dry cleaning establishments now use greater care to protect their employees because of the increasing number of medical publications which have appeared. But the general public needs continued caution as to its danger.

Its poisonous effect can reach the liver by inhalation through the lungs: by absorption through the injured skin; or—as occurs less frequently—by absorption from the digestive tract when it is administered orally. In addition to producing liver damage, it injures the kidneys, upsets the gastrointestinal tract and affects the hematopoietic and the central nervous systems.

Its absorption by the body in large doses produces acute symptoms involving these organs. Some deaths have followed the absorption of overdoses. In the liver there is produced an acute toxic necrosis of the hepatic cells, with a clinical picture and pathological findings similar to those in acute yellow atrophy, or acute hepatitis. The kidneys are affected and show the pathological changes of nephrosis (hemorrhage and fatty degeneration), and albumin and casts appear in the urine, associated with renal subfunction; the gastrointestinal tract becomes inflamed, and nausea, vomiting and diarrhea are commonly observed; the central nervous system is affected, and profound dizziness, syncope, and temporary unconsciousness may occur.

In smaller doses, repeated over long periods, the acute manifestations are less conspicuous but, regarding the liver, the potentiality of carbon tetrachloride is in the production of cirrhosis of the liver. It has been suggested (Davis) that retrograde changes also take place in the kidneys, the hematogenic organs, and in the central nervous system after continued exposure to carbon tetrachloride of low concentrations.

Lamson and his co-workers, and Bollman and Mann, and others have found that by the repeated administration of this substance in appropriate doses for several weeks, they can experimentally produce a condition of the liver of the dog similar to cirrhosis as seen in man.

Carbon tetrachloride (CCl_4) is a saturated chlorine derivative of methane (CH_4) or marsh gas. It is an extremely volatile substance of high specific

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gravity, 1.599, a boiling point of 170.6° F., and a vapor density of 5.33. Thus, this drug is chemically related to chloroform ($CHCl_3$) which is also well known for its effect in producing liver injury.

Davis states that the most frequent uses of carbon tetrachloride now fall into eight groups:

1. As a solvent in the rubber industry.
2. As a solvent in the chemical and drug industry.
3. As a solvent in the paint industry.
4. As a cleansing agent in the dry-cleaning industry.
5. As an occluding and non-oxidizing agent in fire extinguishers.
6. As an anthelmintic for parasites, notably hookworm, in the practice of medicine.
7. In machine shops for the removal of grease.
8. As a dry shampoo in the hair dressing industry, especially in Europe.

A number of cases of acute poisoning following the use of a shampoo containing carbon tetrachloride have been reported, and an occasional death therefrom. Kionka states that the drug is not absorbed through the *uninjured* skin even when applied in large quantities, but Davis says that " carbon tetrachloride extracts the fats from the skin and produces a dry condition which favors absorption and also initiates a dry dermatitis, causing the skin of the hands to crack." Absorption in this manner, as well as by inhalation, might therefore apply to our patient who used a hair tonic containing this drug for a seborrheal alopecia. It might be added that dermatologists in many localities, here and abroad, use this drug for this and other dermatological conditions.

An exact analogy between the histories of carbon tetrachloride poisoning as contained in the literature and the history of the patient here reported is difficult to find. This is due to the fact that in the majority of reported instances poisoning with carbon tetrachloride has been an acute phenomenon, whereas in the present instance the intoxication was in the form of minimal but persistent amounts just sufficient to produce a low gradual intoxication with slowly progressing manifestations. Nowhere in the literature could we find an instance of chronic poisoning in which a similar use of this drug occurred. Knud Møller reports several instances of patients being overcome with acute dizziness and vertigo and temporary unconsciousness after being shampooed with carbon tetrachloride. Presumably the amount of the drug rubbed into the scalp and inhaled by his patients was much greater than occurred in our patient. It is probable that after such acute effects Møller's cases did not return for further shampoos nor was there in his report any long time " follow-up " for after-effects.

But why did not the applier of the shampoo suffer equally to the recipient? The hairdresser in giving a treatment theoretically should absorb as much of the drug through the skin (hands) and by inhalation, and much more frequently when carbon tetrachloride is thus used routinely. Does this not suggest that an individual's susceptibility may play an important part? In our patient we found unusual susceptibility to several drugs: to belladonna or atropine; to caffeine in coffee and to nicotine or the volatile oils in tobacco.

In view of the fact that carbon tetrachloride is used in shampooing, particu-

larly in Europe, one would expect to find similar reported cases. We believe that the absence of such reports is the result of a failure to diagnose the ill effects produced by long application of this chemical. There are already sufficient reports in the literature indicating, both experimentally and chemically, the effects of the absorption of this poison through the skin, particularly when applied repeatedly and over a long period of time, and particularly when reinforced by inhalations during the period of application to the skin.

Case Report

Mr. S. first came under our observation in November 1924 when he was 34 years of age. Over the next 10 years he has been seen many times; on occasions at frequent intervals and at times after an interval of several months. His family and past medical history are unimportant.

His chief complaint has been a diffuse aching pain across the upper abdomen which was first noticed in 1924 and which occurred five to seven hours after his evening meal. It spread upward over an inverted fan-shaped area and centered chiefly in the substernal region. At times the pain-distress was described as a burning sensation, at times as a sense of constriction. It would frequently waken him from sleep between 1:00 and 3:00 a.m., would continue for two to four hours, and was best relieved by heat from an electric pad. At other times the pain was replaced by a sense of upper abdominal fullness and tightness, with distention requiring loosening of belt and clothing. Subsequently (1928 to 1933) he intermittently complained of mild nausea and a distaste for and discomfort after certain foods, especially too heavy protein or fat meals or too bulky vegetables such as cabbage. By degrees certain symptoms, interpreted as toxic effects involving the nervous system, developed, such as loss of mental alertness and concentration, moodiness, nervous irritability, undue fatigability, restless sleep, and mild nausea.

Physical examination in 1924 was not informative save for his sallow color and slight scleral icterus. His liver and spleen were of normal size. There were no telangiectases or hemorrhoids. Cardiovascular disease was not present.

It was not until 1930 that his liver became palpably enlarged to three inches below the costal margin, without explainable cause. He was not addicted to alcohol. There were no foci of infection except in the tonsils and several tooth roots but these were removed during or before 1930, without clinical improvement.

Between 1924 and 1930 it was difficult to feel that this patient was a sick man and we wondered how much neuropsychic disturbance was actually present. However, the patient himself from his own subjective symptoms, which continued despite various plans adopted to control them, repeatedly declared that they were very real and not influenced by his imagination. During this six year interval he had been carefully studied and the following findings were developed:

1. Gastrointestinal roentgen-ray series by Dr. George Pfahler and Dr. Willis F. Manges were not in agreement as to a possible cholecystitis, and biliary drainage evidence did not support this diagnosis.
2. Evidence by roentgen-ray of moderate colon stasis, but without subjective constipation.
3. Nine fractional gastric analyses indicated a persistent achlorhydria, interpreted as a functional disturbance rather than progressive atrophic gastritis because of preservation of rennin and renninzymogen.
4. A mild degree of toxic nephritis was diagnosed because of numerous hyaline casts, a trace of albumin and but 50 per cent elimination of phenolsulphonephthalein in two hours after intramuscular injection. Calcium oxaluria was present on many occasions.
5. A moderate degree of secondary anemia.

In 1930 a suspicion was entertained that these clinical findings might represent the inaugural stages of prepernicious anemia despite absence of stomatitis or noteworthy changes in his blood count. But in 1931 this view was discarded in favor of an early stage of compensated hepatic cirrhosis because of the enlarging liver and particularly so because the patient complained of a marked sense of tenderness and overdistention in the liver region two to three hours after taking tetraiodophthalein during a third roentgen-ray study by Dr. J. Gershon-Cohen. The gallbladder was found to be functioning normally and there was no roentgen-ray evidence of gastrointestinal pathology.

However, neither liver function tests nor blood chemistry have been of much help in this case in estimating liver disease or dysfunction even during the period when the enlarged liver (1930 to 1931) receded to normal size (1932 to 1933) and subsequently became smaller than normal (1934 to 1935).

The direct Van den Bergh reaction has been negative on seven occasions; positive delayed direct reaction occurred only once. Quantitative bilirubin has been above 0.3 mg. per 100 c.c. only twice, reaching 0.6 mg. six days after a tetraiodophthalein dye test in March 1933 and 0.37 mg. in January 1935, at which time the icterus index registered 12.5 units and urobilinogen was present in a dilution of 1 to 40. The patient declined to take a bromsulphalein dye test because of the excessive tenderness of the liver region which had previously followed tetraiodophthalein.

His blood sugar has been constantly on the low side of normal and below normal on two observations; uric acid values have been constantly on the high side or slightly above those for normal; cholesterol readings have been constantly above normal values; urea and non-protein nitrogen were generally above normal.

The amount of liver bile excreted and collectible by duodenal drainage has for many years impressed us as an aid in estimating the function of liver excretion. We have found: first, that healthy young adults yield 250 to 300 c.c. of "C" bile (liver fraction) over a three hour period of actual drainage time, with 200 c.c. representing low normal; second, that in patients with damaged livers (except shortly after an obstructive jaundice has been overcome) recoverable "C" bile drops to less than 150 to 200 c.c. In this patient, during 1924 and 1925, the "C" bile averaged slightly over 50 c.c. Under treatment (carbohydrate diet, decholin and biliary drainage) it increased to 205 c.c. but after an interval of three years dropped back to 145 c.c.

Between 1930 and 1933 our patient's teeth showed progressively interesting changes in pronounced gum recession on the buccal surface (notably Nos. 28, 29, 30 and 31) and by 1933 an erosion of the enamel of the central and lateral incisors had now penetrated through the enamel, with marked flattening of the cusps of the remaining teeth. Coincidentally with this, an arcus senilis noted in 1930 had by 1933 noticeably increased. His gums and mucous membrane were paler than was consistent with his blood count. His color was constantly sallow and his breath distinctly heavy.

It was now evident to us that this patient was suffering from some form of slow intoxication the etiology of which was not apparent at the time of our original examination nor over a period of eight years of discomfort.

In 1933 our attention was attracted to a report of hepatic disturbance following the inhalation of carbon tetrachloride and the possibility of this etiological factor was investigated. It was found that our patient had been using, since 1919 for a seborrheal alopecia, a hair tonic and scalp lotion containing precipitated sulphur suspended in carbon tetrachloride, according to the formula of Prof. R. Sabouraud, the distinguished dermatologist of Paris, and still advocated by him in his various textbooks. This was applied nearly every evening for two or three minutes in a well ventilated bathroom, but it will be noted that untoward symptoms did not develop until 1924, five years later. Despite adequate ventilation the odor of carbon tetrachloride would

persist in his bathroom for an hour after the use of this drug. In addition, it was developed on questioning that carbon tetrachloride was also used as a cleaning agent in his office and that the absorbent cotton, still moist with this chemical, was frequently thrown into the waste basket directly under the nose of our patient. Hence the slow intoxication by this poison absorbed through skin and lungs was accounted for.

In December 1933 we advised that this hair tonic, used more or less regularly for 14 years, should be permanently discarded. Coincidental with this, there occurred (1934 to 1935) the first genuinely subjective improvement in abdominal discomfort and a return of increasing amounts of free hydrochloric acid during gastric analysis and an improvement in blood chemistry. His prior subjective symptoms, as already noted, and a dull ache in recent years chiefly over the liver region, gradually disappeared. He has a more constant sense of well being but he is still unable to "stomach" all foods. He has lessened fatigability but he is still unable to work at high tension without developing an "all gone" sensation in the epigastrium. The mechanism of this can, at most, be but theoretically explained but it may be associated with his hypoglycemia or it is possible that injury to his autonomic nervous system occurred at some time during the period of his slow poisoning.

Objectively, in January 1935, his sallow color is improved. There is no skin and but slight scleral jaundice. He is much more alert, and he seems (and says he is) less "toxic." His teeth are as noted before, except that all cusps have now entirely disappeared. His liver is still definitely smaller than the average normal for his sthenic build. To percussion, the upper border lies at the top of the seventh rib in both the midclavicular and midaxillary lines, and the lower edge does not extend below the rib border. To palpation, at the height of deep inspiration, the liver edge cannot be felt except a small portion of the outer edge of the right lobe. The patient evinces tenderness in forcibly palpating for the liver edge. There are no telangiectases, ascites, or movable dullness, nor have there ever been. So, from start to finish, if the changes in the liver size, the slightly altered blood chemistry and serology, the diminished liver excretion to duodenal drainage, and the somewhat vague symptoms can be considered due to a possible hepatic cirrhosis, it has, except for the subjective disturbances, at all times been well compensated.

Mann and Bollman have had a large experience in studying the effects on the liver of carbon tetrachloride administered by mouth and by inhalation. They find * it difficult to make a direct statement as to the effects of this drug without considerable qualification. They urge careful differentiation between the hepatic cirrhosis of carbon tetrachloride and its acute necrotic effects on the liver which are more like acute yellow atrophy. They find that the cirrhosis is reparative in nature and in the absence of acute effects they are unable to detect any metabolic or functional alterations except in extreme cases. Unfortunately there are usually some renal impairment and disturbances in the gastrointestinal tract which frequently further complicate the picture of carbon tetrachloride poisoning.

Bollman and Mann believe that the alterations of metabolism following acute injury of the liver by such poisoning depend upon the extent of damage to the liver. Bilirubinemia, dye retention, decreased galactose tolerance, etc., are usually present. They find the changes in blood and urine nitrogen are less marked. A slight increase in the uric acid content of the blood is usually found, but no change can be proved in the total non-protein nitrogen, urea, amino acids, ammonia or creatinine, although at times they noted a slight elevation of amino acids and low urea values. The urine may show an increase in uric acid excretion and some increase in amino acids.

* Personal communication.

They do not mention the significance of increased excretion of calcium oxalate in the urine which was noted in the case we are reporting, and which we have noted in cases of suspected liver damage previously studied.

Our patient's definite hypersensitiveness to tobacco smoke was interesting and raises the query as to where in the body is nicotine, or the essential oils or the potassium nitrate in the tobacco or paper of cigarettes, destroyed. Is it in the liver? On closely questioning our patient in regard to such symptoms as he earlier attributed to tobacco smoke, he states that he had not shown any unusual effects in smoking 20 to 30 cigarettes a day until several years after he became exposed to the slow intoxication by carbon tetrachloride as set out above; but subsequently, after being exposed to large quantities of tobacco smoke, as in a business meeting or a smoker, for example, for three or four days thereafter he noted a dull ache in the upper abdomen more frequently in the liver region. This may have been present earlier in his illness than he remembered but he did not attribute it to smoking until a later date at which time he discontinued its use. For several months thereafter he was temporarily relieved of this symptom but he clearly observed recurrences when he attempted to resume moderate smoking or when exposed to heavy or even mild smoking by others.

Summary

In our patient, aside from the changes in the size of the liver, we observed as possible effects of chronic carbon tetrachloride poisoning:

1. Certain symptoms and signs affecting the gastrointestinal tract and the central nervous system.
2. A slight reduction of hemoglobin (70 to 75).
3. A slight reduction of blood pressure (100 to 110 systolic).
4. A tendency to hypoglycemia (75 to 85 mg.).
5. Increased blood uric acid, a substance normally destroyed by the liver (4.3 to 5.2 mg.).
6. Hypercholesterolemia (190 to 345 mg.).
7. An absence of gastric hydrochloric acid (functional).
8. A hypersensitiveness to nicotine or volatile oils in tobacco.
9. Changes in dental enamel and atrophy of the gingiva.

All of these, save the last, were appreciably ameliorated after stopping the use of the hair tonic containing carbon tetrachloride.

We again admit the inability to consider this case as other than a "possible instance" of hepatic cirrhosis produced by very slow intoxication, but we feel that it should be reported because of the difficulty experienced in arriving at this diagnostic impression.

It is probable that borderline cases of chronic intoxication from one or another poison are not so rare as they are unrecognized. By "borderline," we refer to such cases as become diagnostically clear cut as a disease only after gross damage to the viscera has occurred. Then, as a rule, gross chemical changes can be determined by laboratory studies. The real danger lies in classifying many such borderline patients as neuropsychopaths, leading to a too early abandonment of the search for causative factors.

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REPORT OF A CASE OF LEFT VENTRICULAR FAILURE WITH UNUSUAL ANATOMICAL CHANGES IN THE MYOCARDIUM *

By H. Roesler, M.D., and Louis A. Soloff, M.D., *Philadelphia, Pennsylvania*

The recent publications of Weiss [1] and of White [2] have added much to the existing knowledge of the symptomatology of left ventricular failure. Our case is definitely an example of this condition and is the source of added information regarding the pathologic alterations and roentgenoscopic diagnosis.

A 37 year old white man, a clerk by occupation, was admitted to the hospital on February 11, 1933. He had had scarlet fever in childhood, and influenza in 1918. There was no history of rheumatism or syphilis, and a physical examination five years ago was said to be negative. One and one-half years ago he was rejected by an insurance company because of "kidney trouble." He was well until November 15, 1932 when he developed "grippe," but he continued at work until the onset of continuous and marked shortness of breath 10 days afterwards, together with general weakness, perspiration, and great palpitation on exertion. There was never any pain referable to the cardiovascular system. The shortness of breath was especially marked at night and was paroxysmal in character.

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From the Departments of Medicine, Roentgenology and Pathology, Temple University Hospital, Philadelphia, Pa.

On examination the patient suffered from marked dyspnea, orthopnea, and from frequent coughing. There was no cyanosis, no edema, and the liver was not enlarged. A gallop rhythm was visible and palpable. The heart was markedly enlarged to the left, the apex beat being indefinitely felt in the sixth intercostal space three cm. to the left of the midclavicular line. On auscultation a systolic apical murmur and a well developed mid-diastolic gallop rhythm were heard all the way from the apex to the epigastric notch. The aortic second sound and the pulmonic second were equally intense. Small moist râles were present at both bases. The rhythm was regular with a rate of 110. The blood pressure at the time of admission was 220 systolic, and 120 diastolic. A few days later it was 164 systolic and 106 diastolic. The temperature was normal. The blood counts were normal, as were also the blood chemistry examinations. The urine showed a trace of albumin and occasionally a few hyaline casts. Examination of the kidney function revealed practically normal findings. The Wassermann-Kolmer and Kahn reactions were negative. The electrocardiogram showed regular sinus rhythm, a slight degree of left axis deviation; and the T-wave was isoelectric or diphasic in all three leads, con-

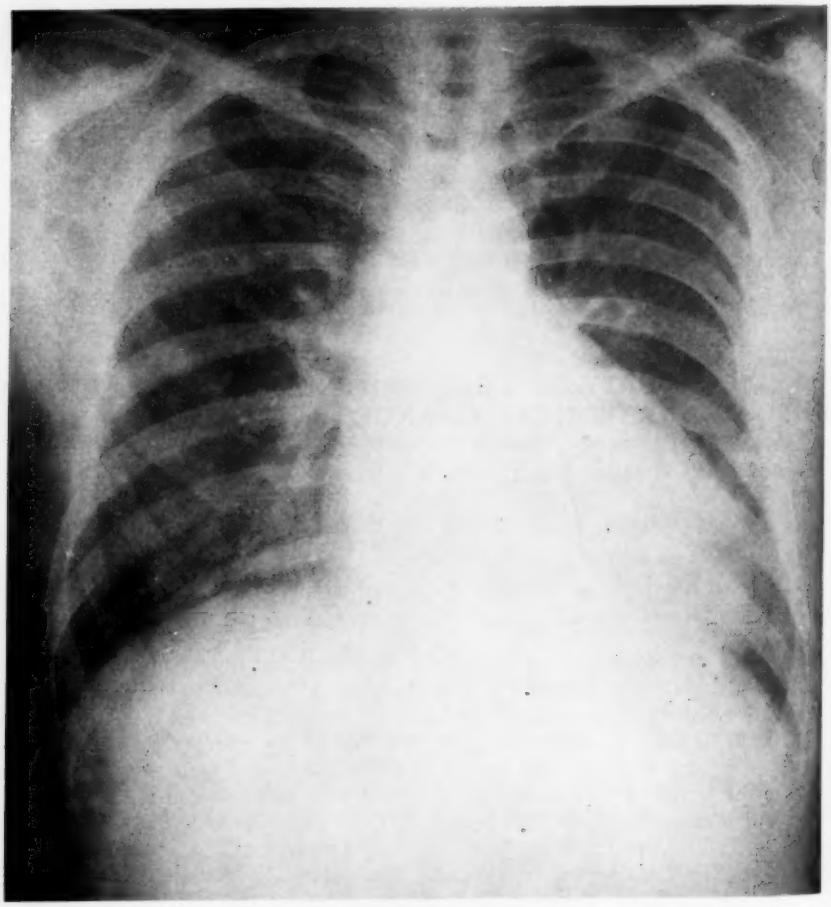

FIG. 1. Roentgenological appearance of the chest at the time of the first examination of the patient, 2-13-33.

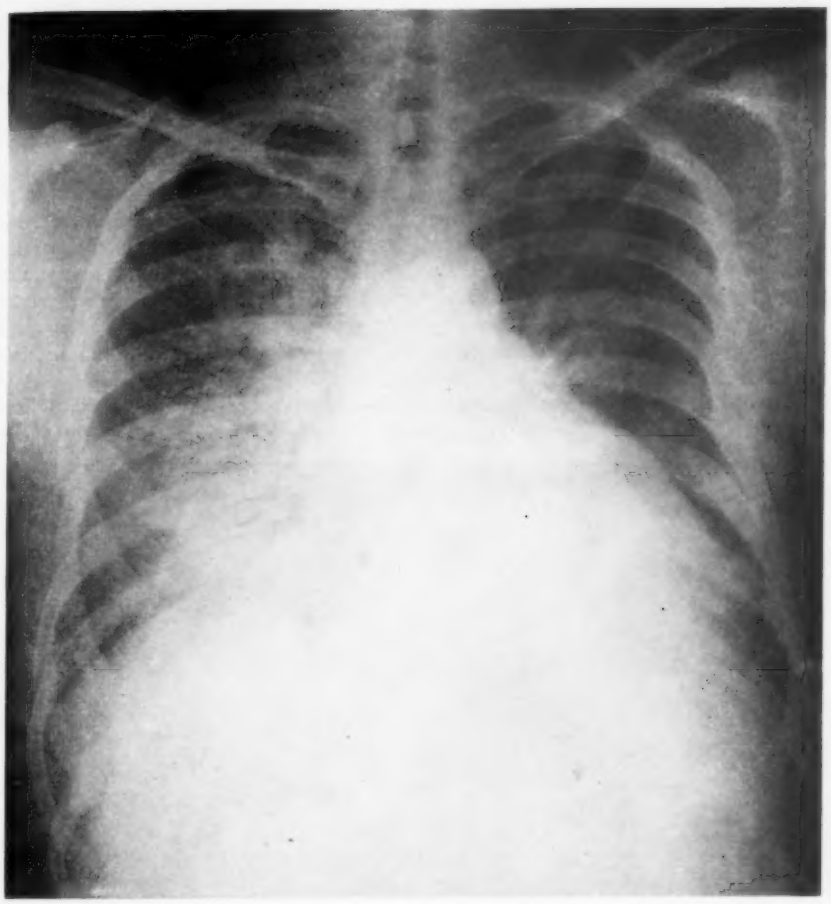

FIG. 2. Roentgenological appearance of the chest when the patient showed very pronounced symptoms and signs of left ventricular failure, 3–7–33.

stantly so upon repeated examinations. On roentgen-ray examination, a marked enlargement of the heart to the left and posteriorly, corresponding to the left ventricle, was made out. The left atrium showed no appreciable changes. There was a moderate amount of congestion in the lungs, especially in the central portions of the right lung. The amplitudes of pulsation as revealed by fluoroscopy were small.

On February 26 the patient developed an upper respiratory infection with fever. Shortly afterwards appeared cyanosis, hemoptysis with foamy blood, marked sweating, attacks of cardiac asthma at night, an increase in râles throughout the lungs, a marked accentuation of the pulmonic second sound, and some enlargement of the liver. The gallop rhythm became more marked. There was improvement, but after about two weeks another relapse, a new period of improvement and finally a continuous stage of heart failure with but little peripheral edema. During the last 15 days the maximum temperature was 101° F. Very marked congestive lung failure was present and a right pleural effusion was aspirated. During the course of the whole illness, there was a tendency for the blood pressure to fall; it reached 110 systolic and 90 diastolic a few days before death. The urea nitrogen exceeded the normal limit within the last

weeks and reached 29 mg. per 100 c.c. The gallop rhythm was always present but almost completely disappeared several times following morphine injections. The electrocardiogram showed no fundamental changes. Repeated roentgen-ray films were made. The heart size showed no noticeable change. Remarkable were the changes in the degree of pulmonic congestion. A definite parallelism could be observed between decrease or increase of this and the clinical signs and symptoms of improvement or relapse. Only three pictures of the follow-up series are given (figures 1, 2, 3). It is noticeable that the central portion of the right lung appears of increased density, has a patchy, mottled, cloudy, confluent appearance which fades out hazily into the more peripheral portions. The corresponding changes in the left lung are almost completely hidden by the heart shadow, especially so because of the high position of the diaphragm. The periphery of the lung fields shows relatively good transparency.

During the course of the illness digitalis, strophanthin, salyrgan, metaphyllin and glucose were given.

The clinical diagnosis was: Etiological—hypertensive cardiovascular disease;

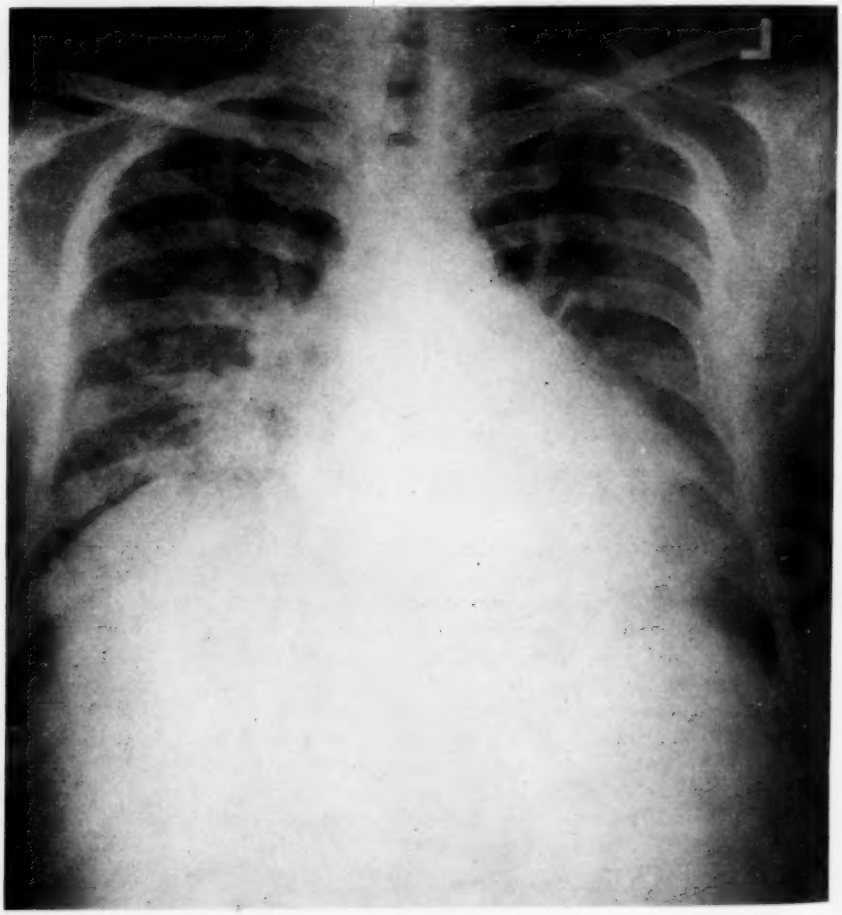

FIG. 3. Roentgenological appearange of the chest about two weeks later, 3-24-33. Clinically improved.

respiratory infection. Anatomical—left ventricular hypertrophy and dilatation. Coronary artery disease with possible occlusion of the left coronary orifice. Bronchopneumonia. Physiological—regular sinus rhythm, hypertension, left ventricular failure.

Autopsy. The patient died on April 28, 1933. Necropsy was performed three hours after death: There was but a moderate edema of the lower extremities and also of the sacral region. The abdominal cavity contained slightly more than two liters of light amber fluid. The liver extended for eight cm. below the right costal margin in the mid-clavicular line. The upper half of the left pleural cavity was obliterated by firm fibrous adhesions. The lower half was obliterated by fibrinous adhesions which were separated with some difficulty. The entire right pleural cavity was obliterated by similar adhesions. These extended over the diaphragmatic surface where on the inner third was located a small pocket containing about 60 c.c. of light amber fluid. A large hemorrhagic infarct was present in the right upper lobe. The right middle and lower lobes were completely consolidated. The left lower lobe was almost completely solidified. The spleen and liver were enlarged and the seat of marked chronic passive congestion. The kidneys showed markedly arteriosclerotic and arteriolosclerotic changes. The pericardium contained about 100 c.c. of amber fluid, and the lining was smooth and glistening. The heart weighed 650 grams. The epicardium was glistening and transparent except for a few fine shaggy threads of fibrin over an area measuring two cm. on the middle of the anterior surface of the heart. There was very little subepicardial fat. The myocardium was moderately firm and dark red-brown. The incised surface contained many long and broad gray streaks. There were many circumscribed gray patches one to two mm. in diameter in the left ventricle. Only the mitral valve leaflets appeared altered and they were very slightly thickened. The sinuses of Valsalva contained a few atheromatous plaques, more prominent in the left aortic sinus surrounding the orifice of the left coronary artery. The descending and circumflex branches of the left coronary artery left the aortic sinus separately. Their orifices were definitely constricted as compared to the lumina distal to them. Dissection of these branches and of the right coronary artery revealed them to be patent, with a rare yellow fatty or atheromatous plaque. The circumference of the right coronary artery was one cm., that of the descending branch of the left coronary 1.1 cm., and of the circumflex branch 0.9 cm. The orifice of the descending branch was 0.6 cm. in diameter, and of the circumflex branch 0.5 cm.

Microscopic Description: Representative sections of the left and right ventricle were studied. They were stained with hematoxylin-eosin, Van Gieson, Verhoeff, and Gram stains. The left ventricle presents a remarkable, striking appearance. There are regions in all sections (figure 4) occupying approximately an entire low power field characterized by a complete disappearance of muscle bundles which has left a fine meshy reticular or lace-like structure. Under higher power (figure 5) this is seen to be made up of fibrils containing no cytoplasm, or with clear unrecognizable cytoplasm, and a slight infiltration of macrophages, occasional lymphocytes, and rarely, polymorphonuclear leukocytes. The cellular reaction in the interior of these lesions is unusually slight. As the periphery of the lesions is approached, the various stages through which it must have gone are seen. Many muscle fibers are seen lying free in the center of spaces lined by similar fibrillar lace-work. Many of these fibers have no nuclei, others are completely hyalinized. All have at least obscure striations. More peripherally, hyalinization and acute degeneration of the muscle become prominent. It is interesting to note, that as one examines from the fibrillar network outward toward the more normal appearing musculature, the cellular reaction becomes more intense and of a different character. Within the fibrillar lesion the macrophage predominates; at the periphery of these lesions, the lymphocyte, and in the musculature itself, the neutrophilic polymorphonuclear leukocyte. The muscle fibers are

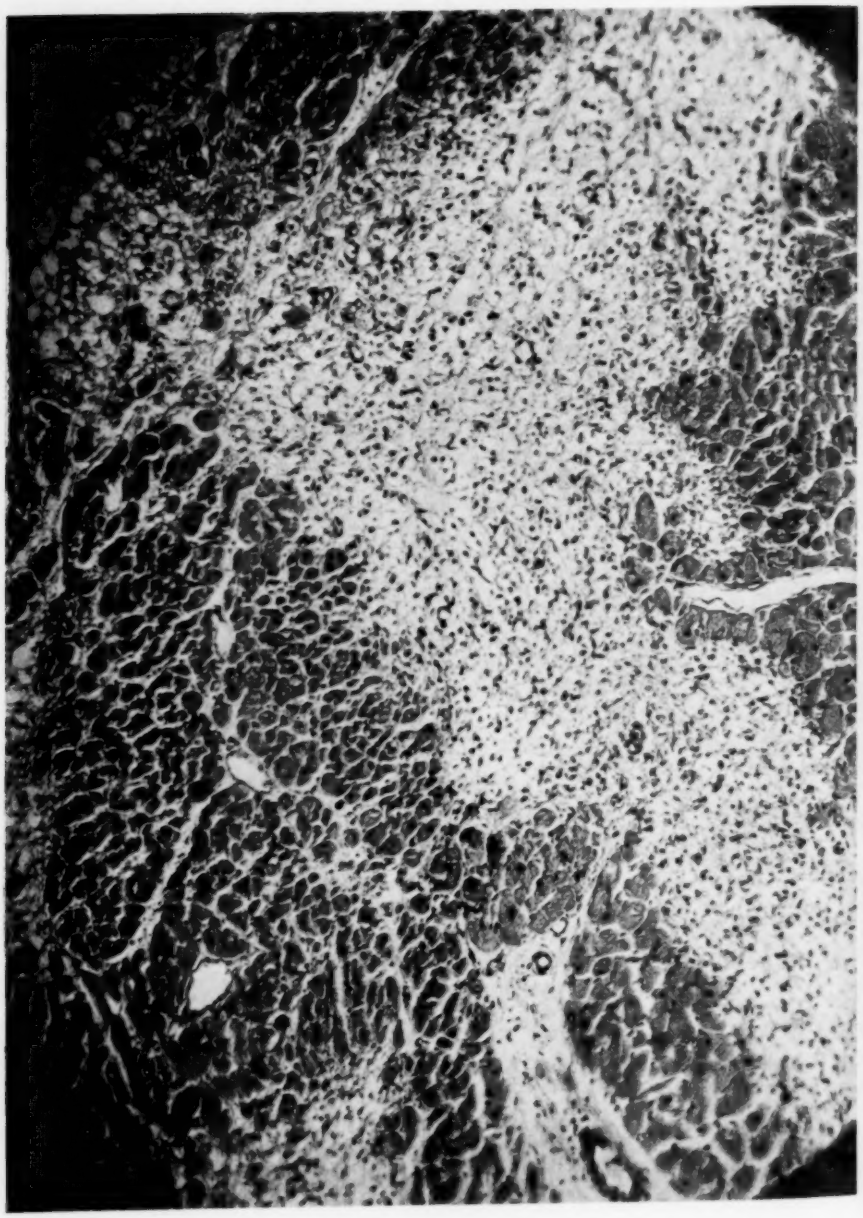

FIG. 4. Left ventricular wall, low power, showing the characteristic distribution of the focal lesion.

FIG. 4. Left ventricular wall, low power, showing the characteristic distribution of the focal lesion.

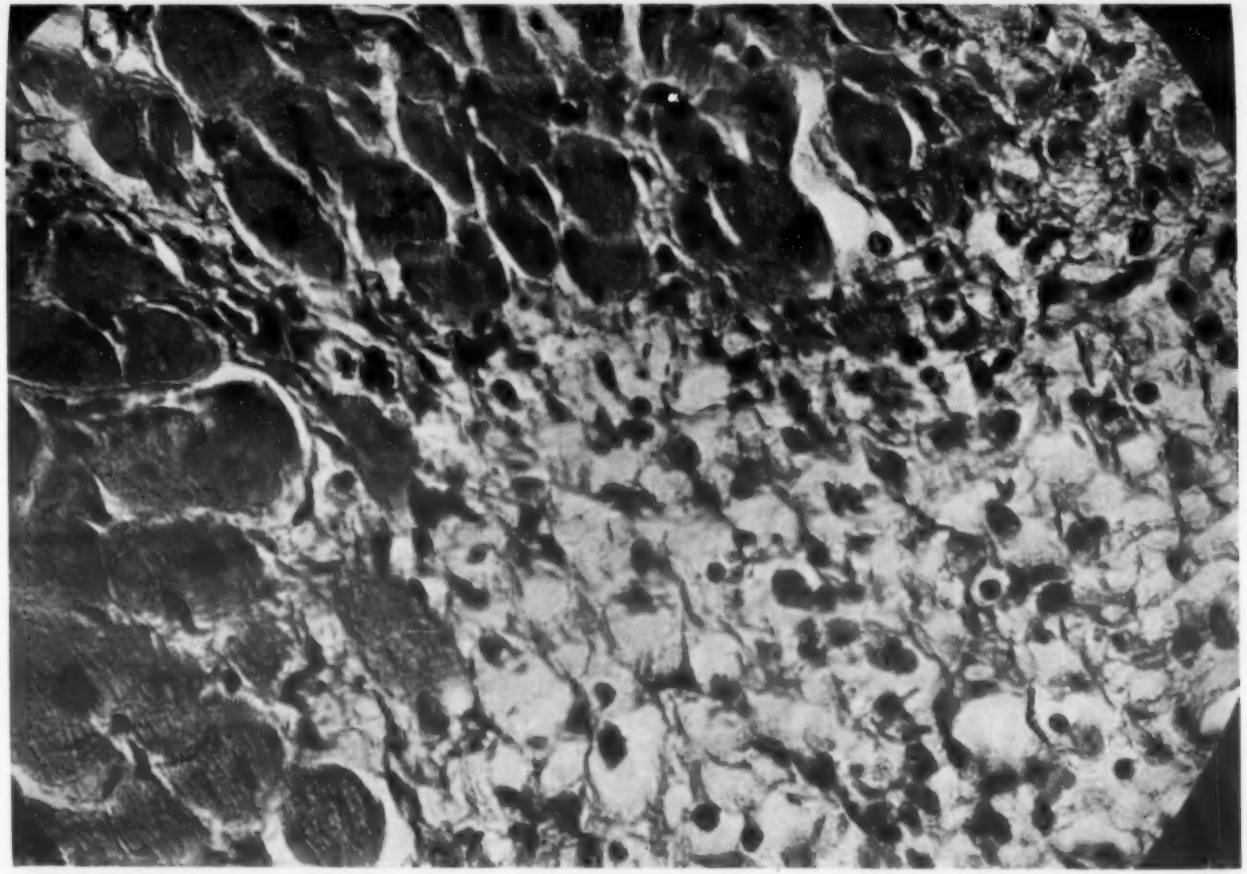

FIG. 5. Left ventricular wall, high power, illustrating the complete loss of muscle fibers.

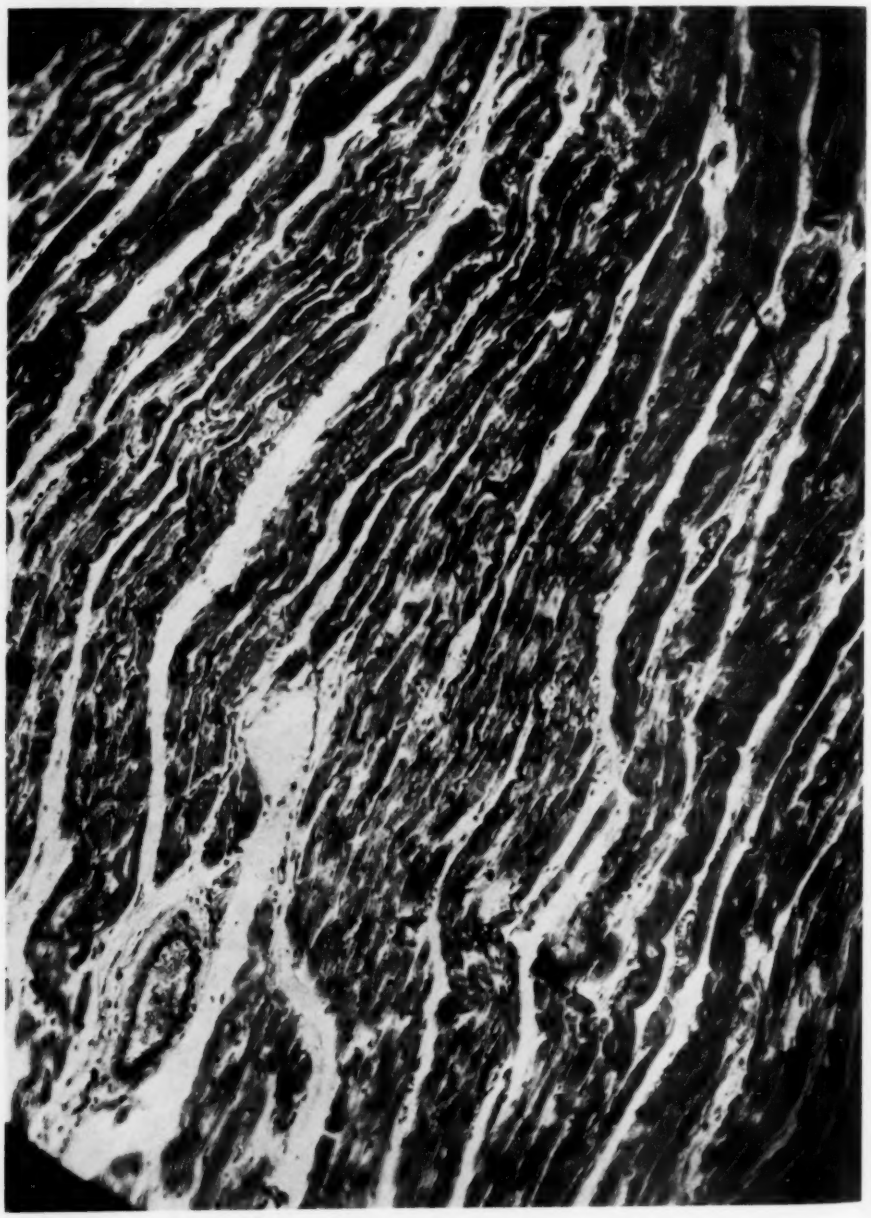

FIG. 6. Right ventricular wall.

distinctly larger than normal. The coronary vessels present nothing noteworthy except that they are dilated. It is probably significant that the focal fibrillary lesions are everywhere situated farthest from the coronary branches. The interstitial tissue of the hypertrophied musculature is increased. There are many regions of fibrosis and a mild exudate of polymorphonuclear leukocytes, plasma cells, lymphocytes and occasional macrophages. No bacteria were found. None of the sections of the right ventricle contains these lace-like lesions (figure 6). Except for a moderate hypertrophy of the musculature and perhaps a very slight fibrosis, the right ventricle presents nothing remarkable. On postmortem blood culture pneumococci (type III) were grown.

Pathologic Diagnosis: Hypertrophy of the heart, particularly of the left ventricle. Acute degeneration of the myocardium. Fibrosis of myocardium. Subacute myocarditis with focal fibrillar fibrosis of left ventricle. Anomalous left circumflex artery. Mild arteriosclerosis of the coronary arteries and aortic sinuses. Stenosis of the orifices of the circumflex and descending branches of the left coronary artery. Mild fibrinous pericarditis. Mild atherosclerosis of the aorta. Fibrous adhesions, left upper lobe of lung. Pneumococcic pneumonia, right upper and middle lobe and left lower lobes. Encapsulated right diaphragmatic fluid. Subacute fibrinous pleuritis with granulation tissue. Arteriosclerosis and arteriolosclerosis of kidneys. Infectious hyperplasia with chronic passive congestion of spleen. Chronic passive congestion with mild central necrosis of liver. Ascites, dependent edema, icterus.

Two unusual features of this case might be emphasized: the unusual microscopic findings in the heart muscle, and the roentgenoscopic appearance of the lung fields.

Among the causes of this man's illness were hypertension, arteriosclerosis and arteriolosclerosis of the kidneys and myocardial hypertrophy with mild fibrosis. The respiratory infections, and especially the pneumococcic pneumonia, probably precipitated cardiac failure. The peculiar lesion limited to the left ventricle, appears unique. It resembles no other type of myocardial lesion with which we are familiar. That it is not infectious is shown by the absence of bacteria in the myocardium. We believe it is probably toxic. It is speculation to relate it to the upper respiratory infections at the beginning and during the course of the patient's sickness, or only to the pneumococcic pneumonia, or to both of them. We distinguish sharply the fibrosis due to the old hypertensive renal lesion and the subacute myocardial lesions. We have already remarked that the focal fibrillar lesions are situated at the greatest possible distance from the coronary branches. This suggests some relationship between the focal lesions and the blood supply. It is obviously not a question of sclerosis of the coronary branches, which was very slight in this case. It may, however, have something to do with the ability of the musculature to rid itself of its toxins which probably is more difficult in those regions where the blood supply is least. This may perhaps have some relationship to the unilateral character of the lesions,—its absence from the right ventricle being due to the thinness of its wall and perhaps better blood supply. The stenosis of the orifices of the left coronary branches may have some relation to the blood supply to the left ventricle, but we must admit that we have seen many cases of marked constriction of the coronary orifices and infection without similar lesions.

As to the roentgenologic aspect, various types of congestive lung failure have been observed. One type of congestive lung failure, as for instance seen in chronic mitral valvular disease, is fundamentally characterized by its diffuse distribution. Anatomically, the blood vessels as well as the lymphatics are di-

FIG. 6. Right ventricular wall.

lated. A certain degree of induration, due to fibrosis, as well as of transudation is present, the latter especially around such foci of consolidation as old tubercles, scars, areas of atelectasis, and in the dependent, less aerated portions. In considering these main factors we observe in the film a general haziness with marked increase of the normal lung detail as well as a tendency to an appearance of diffuse fine mottling which occasionally is miliary in character. Quite different is the appearance in certain subacute or acute forms of disturbance of the hydrodynamic conditions in the lung, the most marked type being represented by the acute edema of the lung. Acute nephritis and failure in coronary arterial disease with hypertension are the best-known examples. From a roentgenologic viewpoint, the changes are less " vascular " in appearance. In other words, the appearance of the lungs in the present case cannot be accounted for on the basis of enlargement of blood vessel shadows as projected in longitudinal, oblique and transverse sections upon the film, with characteristic decrease of density and dimensions as the peripheral parts of the lung fields are approached. The usual appearance in this type of a case is a diffuse or mottled-patchy consolidation, the borders of which fade out rather rapidly into the surrounding lung area. Interstitial transudation, sometimes of a diffuse character, located around the central portion of the lungs, dominates the picture. As a matter of fact the apical and axillary portions remain remarkably free of these changes. Those lung portions where the active arterial filling is better, seem to be preferred. The right lung is usually more affected, which is to be compared with the generally greater tendency to right-sided pleural transudation. These changes can appear and disappear within a remarkably short time, as contrasted with the chronic changes in the lungs most typically observed in chronic mitral valvular lesions. They also may exist, in minor degrees, without giving characteristic auscultatory signs.

The observation of the roentgenologic appearance of the right lung field in this case could merely correspond to a pneumonic process. The histologic appearance, however, permitted us to estimate the duration of this process to be about two weeks and from a clinical viewpoint, fever was not present until 15 days before death occurred. The films showing the characteristic changes in question were taken seven weeks before death. Secondly, the change in the roentgenologic appearance was closely interrelated with the degree of cardiac decompensation. And finally, similar roentgen-ray pictures as observed in the course of cardiac decompensation, have been published by Zdansky, Chapman, Korns, Coe and Otell.

We have submitted the microscopic slides to Drs. C. Sternberg of the University of Vienna; W. Koch, of the University of Berlin; G. B. Gruber and W. Putschar, of the University of Goettingen, and wish here to express our thanks for their kind and valuable assistance.

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EDITORIAL

SURGICAL PROCEDURES IN ESSENTIAL HYPERTENSION *

The early work of Claude Bernard on the discovery of the vasomotor nerves was an event of tremendous importance. The application of this knowledge to problems in clinical medicine was delayed for half a century. The past decade has demonstrated in a most convincing fashion that, in man, removal of the sympathetic ganglions is followed by permanent vasodilatation of the arteries of the extremities. This has also been demonstrated in the experimental animal by exact quantitative methods. The thermostromuhr method of Rein, thermometric readings in the deep and superficial tissues, have furnished controlled experimental evidence of this fact. Equally convincing have been the clinical observations in man. It may be stated at present, that with the complete removal of the appropriate sympathetic ganglions, permanent vasodilatation is produced in the lower extremities. In the upper extremities, sympathetic ganglionectomy does not affect prolonged vasodilatation in the same degree as it does in the lower extremities. The explanation of this difference is not clear. A logical result of this work was the attempt to apply operative procedures on the sympathetic nervous system in an attempt to control essential hypertension. The modern conception of the fundamental abnormality of this disease is that there is an inherited hypersensitivity of the vasomotor mechanism and that this defect is demonstrable in early years of life in children of hypertensive parents. This hypothesis carries with it the implication that the heightened responses in the blood pressures lead to hypertrophy of the *tunica muscularis* and increase in the blood pressure. Interruption of the vasomotor nerve supply of a large section of the arteriolar bed would theoretically modify or reduce these vasomotor reactions and decrease the blood pressure of subjects in whom the organic changes were not too advanced.

Among the various surgical procedures which are being tried are certain which involve the suprarenal glands. These operations are based on the hypothesis that increased amounts of epinephrine are concerned with the production and maintenance of essential hypertension. A tremendous amount of experimental evidence has given no basis for this conception. Physiologic studies seem to prove that the products of these glands are concerned with emergency functions and not with sustained effects. Denervation of the suprarenal glands has been carried out without evidence that the levels and responses in blood pressure are materially changed. It must be realized that complete denervation, as carried out on the suprarenal glands of man is most difficult and probably impossible. Partial resection of the suprarenal glands has been advocated. A critical survey of the effects of this operation would seem to indicate that the decrease in blood pressure may be secondary to a very definite systemic weakness, which may follow this

* Submitted for publication September 11, 1935.

procedure. It is probable that the control of hypertension by operative measures on the suprarenal glands should not in our present state of knowledge be viewed too optimistically.

Operations on the sympathetic nervous system seem more logical and are engaging the attention of many workers. There are two types, resection of the splanchnic nerves either by supradiaphragmatic or infradiaphragmatic approach. The immediate and remote results of these operations are at present *subjudice*. Symptomatic improvement of the headaches, which are caused by the hypertension, and the general feeling of well-being have been noted. A significant decrease in the blood pressure when the patient is in the upright posture, and persistent lowering of levels and responses for long periods have not been conclusively demonstrated. This operation is carried out in two stages and entails a low risk. A more drastic operation is that of anterior rhizotomy, in which complete removal of the preganglionic sympathetic fibers below the fifth thoracic segment is accomplished by resection of the anterior roots from the sixth thoracic to the second lumbar nerves, inclusive. This procedure is followed by a loss of function of the sympathetic nerves below the diaphragm. All vasomotor fibers to the suprarenal glands, kidneys, abdominal vessels, and those to the lower extremities are interrupted. There is loss of sweating below the costal margin. Complete denervation of the splanchnic vessels is evinced by the sharp decrease in blood pressure that occurs when the patient is in the standing posture. The immediate effects within periods of one to three months after operation are dramatic. The value for the blood pressure decreases sharply to less than 100 mm. of mercury when the patient is in the standing posture. Symptoms are relieved and dilatation has been observed in the arterioles in the retina. The ultimate effects of this operation are yet to be determined. The applicability of this operation would, necessarily, be limited to the more severe forms of hypertension which affect the younger age groups, that is, those which affect patients who are less than forty-five or fifty years of age. The prognosis in these cases may be as grave as that of malignant growths. In this group, any procedure that would modify or delay the inevitable outcome is eminently justifiable. Careful selection of patients is important and those with renal, cardiac, or cerebral insufficiency should be excluded. The operation is one of some magnitude but no more so than many other operations that are attempted to control malignant disease. It has been carried out in two stages, thereby reducing the risk. There is some reason to hold an optimistic view of the ultimate value of such procedures in the treatment of hypertension. Careful and critical observations on the changes in blood pressure following operation are highly important. The evaluation of changes in the vasomotor function, as studied by the blood pressure, is at best difficult and beset with error. The supposed beneficial effects must be definite and prolonged. Studies must be carried out for long periods. The most significant single test for loss of the vasomotor splanchnic control is the postural decrease in blood pressure that occurs when the patient is in the upright posture.

GEORGE E. BROWN

REVIEWS

Clinical Laboratory Medicine and Diagnosis. By R. B. H. GRADWOHL, M.D. 1028 pages; 18 × 26 cm.; 328 illustrations, 24 color plates. First Edition. C. V. Mosby Co., St. Louis. 1935. Price, $8.50.

This work is a most admirable one in the field of diagnosis, and especially laboratory diagnosis. It covers the usual divisions of clinical pathology, as urinalysis, blood chemistry, hematology, gastric analysis, analysis of feces, sputum and punctate fluids. It devotes a chapter to pathology and exotic pathology, and one chapter each to special tests for rabies, allergy, pregnancy tests, chemical milk examination, mycological diagnosis, autogenous vaccines and semen appraisal. There is a chapter each on bacteriology, serology, basal metabolic determinations, postmortem examination, tissue cutting and staining, preparation of museum specimens, and on toxicological technic.

The author draws from an extremely wide personal experience, both from his own laboratories and from the laboratories of others. According to the record, he began the study of pathology some 35 years ago. He studied abroad under such renowned masters as Virchow and Langerhans of Germany and Chiari of Austria; and one can feel the influence of the Continental schools, chiefly the Germanic, woven into the work. An extremely large share of the references are to the German medical literature, and some of the illustrations are reproductions of German originals.

Some of the 18 chapters are rather abbreviated, as for instance the chapter on sputum which is condensed into seven pages, and the chapter on gastric analysis which is only 21 pages in length. Other chapters, however, cover their subject rather exhaustively, as for instance the chapters devoted to hematology and bacteriology and bacteriological applications to clinical diagnosis. Both of these deserve special mention because of outstanding merit; and together they occupy 336 pages. Any disappointment over the brevity of certain sections or whole chapters is compensated by the adequacy of the treatment of major topics.

The 352 illustrations and plates aid greatly in clarifying the text. Of these about 250 are original illustrations and color plates and about 102 are reproductions from other works and authors. The 24 color plates are well done.

One may say with justice that this book represents the life work of its author in a large and varied medical field. It is much more pretentious than some of the recent short-cut works in clinical pathology. It combines clinical pathology, pathology, histology, and postmortem study with bedside diagnosis. And while some of the sections are somewhat outdated by more recent work, it may be considered an extremely valuable book which deserves a prominent place in the general library or for ready reference on the laboratory desk.

S. L. J.

Blood Groups and Blood Transfusion. By ALEXANDER S. WIENER, A.B., M.D. xiv + 220 pages; 17 × 26 cm. Charles C. Thomas, Baltimore. 1935. Price, $4.00.

Few will question the statement that this book will immediately become the acknowledged English text on Blood Groups. Unlike many who may be complete masters of a complex subject but are singularly inept in teaching first principles, Wiener has happily achieved a treatise which is primer-like in its exposition of material to the beginner. Yet the student will find, in addition, all the wealth of investigative work leading up to our present knowledge of this intricate subject. After a thorough review of the four blood groups, the subgroups of group A and AB and

the agglutinogens M and N of Landsteiner and Levine are presented in great detail and with remarkable clarity. The latter half of the book deals largely with investigations into the genetic, biometric and anthropological aspects of the blood groups, and finally there is a very lucid exposition of their medico-legal applications,—in which latter field, of course, Wiener is an acknowledged master.

The chapters on Blood Transfusion are not exhaustive but, on the whole, are adequate. The last few years have seen a very marked decrease in the incidence of post-transfusion reactions of the so-called "foreign body" type. The recognition that they can be practically eliminated by proper routine cleansing of apparatus and preparation of solutions is now widespread. These facts, while not omitted, have hardly been sufficiently stressed. Some of the newer and popular direct transfusion apparatuses have been omitted.

The general excellence of the book, however, overshadows any minor faults and it may truthfully be said that to the student of blood groups this book is unique and invaluable.

H. R. P.

The Story of Medicine in the Middle Ages. By DAVID RIESMAN, M.D., Sc.D., F.A.C.P., Professor of the History of Medicine and Professor Emeritus of Clinical Medicine, University of Pennsylvania; Member, History of Science Society and Medieval Academy of America. xii + 402 pages, 79 illustrations. Paul B. Hoeber, Inc., New York. 1935. Price, $5.00.

It required courage as well as insight and industry to write *The Story of Medicine in the Middle Ages.* Most medical historians have passed lightly over the period which has disparagingly been called the Dark Ages, and its achievements have been overlooked or minimized. Then, too, the historian was under necessity of placing temporal limits upon the period with which he dealt. For the beginning of the Middle Ages, dates as varied as that of the birth of Christ and of the crowning of Charlemagne, 800 years later, have been proposed. As to the termination of the period, the arresting suggestion that we may still be in the Middle Ages is not without some basis, although doubtless it will be accepted with the tolerant chuckle with which it was given. For each of many recent generations the "Middle Ages" has signified an indefinite period somewhat remotely antedating the epoch of its own naively egotistical superiority. Dr. Riesman follows most modern historians in assuming that the Middle Ages ended several centuries ago.

Not once does *The Story of Medicine in the Middle Ages* become a tiresome chronicle. After a number of chapters dealing with the Greek inheritance, the monastic influence and the part played by Arabian and Jewish physicians, the schools of medical thought are discussed. Then is described the rise of the universities, perhaps the most important factor in the development of modern culture. Of these there were at least eighty, but Montpellier, Bologna, Padua, Paris and Oxford and Cambridge were of special importance in medical matters. These provide chapter headings. The growth of the divisions of medical thought—anatomy, surgery and sanitation—is traced and the extraordinary epidemics, some of which are even today imperfectly identified, are described. The evidence for and against the American origin of syphilis is assembled and condensed. While definite decision is withheld, the author may be suspected of inclining to the anti-American opinion. The free use of quotations from original sources and abundant references in footnotes make this a well-documented text for the student of medical history; but its interesting material and lively style recommend it also to the general reader.

Dr. Riesman concludes that the Middle Ages possessed three outstanding advantages that no longer obtain: one dominant religion, one social system, one universal language. Two other characteristics, of lesser importance, were the distinction

conferred by scholarship and the abundant opportunity for poor scholars to achieve an education. "The greatest difference between modern times and the Middle Ages, in medicine as well as in all sciences, is the objective, the experimental method."

C. V. W.

Amebiasis and Amebic Dysentery. By CHARLES F. CRAIG, M.D. 315 pages; 17 × 25.5 cm. First Edition. Charles C. Thomas, Springfield, Ill. 1934. Price, $5.00.

This is a complete treatment of the subject of amebiasis and amebic dysentery, by a well known authority in this field. The 12 chapters cover the etiology, epidemiology, pathology, symptomatology, complications and sequelae, diagnosis, complement-fixation test, prognosis and prophylaxis, and finally the treatment of the disease. Each one of these 12 chapters concludes with an extensive bibliography.

This book was most timely, appearing as it did very shortly after the outbreak of amebic dysentery following the Chicago World Fair. Its lasting usefulness, however, is well assured, for according to the statistical figures, contained in the chapter on epidemiology, between 5 and 10 per cent of the population of the United States harbor the ameba at some time in their life. If these figures are accepted it would mean that between six and twelve million people in this country are potential amebic patients.

Dr. Craig has written a valuable monograph on an important subject. It will be useful not only to the parasitologist and the clinical pathologist but also to the internist. There is a very adequate discussion of the symptomatology and of the complications of amebic dysentery and a conservative evaluation of the many types of therapy which have been proposed. The author's views as to the clinical effects of amebiasis without outspoken dysentery are of great interest.

S. L. J.

Physical Diagnosis. By WARREN P. ELMER, B.S., M.D., and W. D. ROSE, M.D. 919 pages; 15.5 × 23.5 cm. C. V. Mosby Co., St. Louis. 1935.

The seventh edition of Elmer and Rose's "Physical Diagnosis" constitutes a further improvement of this excellent textbook. The excellent chapters on clinical anatomy and physiology are very clearly written and splendidly illustrated. The larger part of the following text is given over to physical diagnosis as applied to the respiratory and circulatory systems. These are very adequately dealt with. The essentials of physical diagnosis in other regions of the body than the chest are also covered. Laboratory methods of diagnosis are not included.

The book is well bound; the type is large; the illustrations are well chosen. It deserves widespread use.

T. C. W.

COLLEGE NEWS NOTES

Dr. H. R. M. Landis (Fellow), Philadelphia, is Associate Director in charge of the clinical and sociological departments of the Henry Phipps Institute of the University of Pennsylvania.

Dr. George W. Grier (Fellow), Pittsburgh, was installed as President of the American Radium Society at its annual meeting in Atlantic City.

Dr. Olin S. Allen (Fellow), Wilmington, Del., is a member of the Medical Council of Delaware.

Dr. Chester M. Jones (Fellow), Boston, and Dr. Russell S. Boles (Fellow), Philadelphia, became President-Elect and Secretary, respectively, of the American Gastro-Enterological Association at its last annual meeting.

Dr. Edward S. Sledge (Fellow), Mobile, Ala., has been made a Vice-President of the Chattahoochee Valley Medical Association.

Dr. Francis W. Heagey (Fellow), Omaha, Nebr., has been elected President of the Nebraska Tuberculosis Association.

Dr. Kenneth M. Lynch (Fellow), Charleston, S. C., has been appointed to the State Board of Health, succeeding Dr. Robert Wilson (Fellow), resigned.

Dr. David W. Carter (Fellow) and Dr. Homer Donald (Fellow), both of Dallas, Tex., have been made President and Treasurer, respectively, of the Dallas Southern Clinical Society for the ensuing year.

Dr. George Fordham (Associate), Powellton, W. Va., has been elected President of the West Virginia Society of Industrial Physicians and Surgeons.

Dr. Walter C. Swann (Fellow), Huntington, Dr. A. H. Stevens (Fellow), Fairmont, and Dr. R. J. Condry (Fellow), Elkins, have been made President, Vice-President and Secretary, respectively, of the West Virginia Heart Association.

Dr. Fritz B. Talbot (Fellow), Boston, has been elected President of the American Pediatric Society for the ensuing year.

Dr. James W. Hunter (Fellow) and Dr. Walter B. Martin (Fellow), both of Norfolk, have been installed as President and President-Elect, respectively, of the Norfolk County Medical Society.

Dr. James J. Waring (Fellow), Denver, Colo., has been elected President of the National Tuberculosis Association.

Dr. Charles J. Bloom (Fellow), New Orleans, La., has been elected President of the Louisiana State Pediatric Society.

Dr. James B. Collip (Fellow), Montreal, Que., Dr. Elliott P. Joslin (Fellow), Boston, and Dr. O. H. Perry Pepper (Fellow), Philadelphia, hold membership on the Board of six scientists appointed as an advisory council to the George S. Cox Medical Research Institute of the University of Pennsylvania. The Institute was founded in 1932 with a fund provided under the will of the late Mr. Cox, a Philadelphia banker and manufacturer. The council will hold annual meetings to receive reports, review work of the Institute, which is devoted to the study of diabetes, and to consult with the staff on further investigations.

Dr. John S. Hibben (Associate), Pasadena, Calif., was installed as President of the American Congress of Physical Therapy at its meeting in Kansas City, September 9 to 12.

Dr. Isaac Hall Manning (Fellow), formerly Dean of the University of North Carolina School of Medicine, is President of the recently organized Hospital Savings Association of North Carolina. Among the directors are Dr. Paul P. McCain (Fellow), Sanatorium, President of the Medical Society of North Carolina, and Dr. Louis B. McBrayer (Fellow), Southern Pines, Secretary of the Medical Society of North Carolina.

Dr. Guy H. Turrell (Fellow), Smithtown Branch, L. I., N. Y., has been elected Secretary of the New York State Sanitary Officers' Association.

OBITUARIES

DR. HARRY WINFRED GOODALL

Dr. Harry Winfred Goodall died April 17, 1935, at Boston, Massachusetts, in his fifty-eighth year.

Born in Wells, Maine, the son of George B. and Isabel M. (Norton) Goodall, he attended the Berwick Academy and received his A.B. at Dartmouth College where he was awarded the Grimes Prize and became a member of Kappa Kappa Kappa. In 1902 he was graduated *summa cum laude* from the Harvard Medical School. Following a two year internship at the Massachusetts General Hospital, a service at the Boston Lying-In Hospital, an assistant residency at the Massachusetts General, he began in 1904 the practice of medicine. In 1908 Dr. Goodall pursued advance studies at the University of Tübigen in Germany.

Dr. Goodall was at one time lecturer on digestive diseases at the Dartmouth Medical School as well as instructor in chemistry at the Harvard Medical School. He served during the World War both in this country, at Camp Greene, North Carolina, and Camp Wheeler, Georgia, and overseas as commanding officer of the gas hospital at Toul, France, and as chief of the medical service at Base Hospital No. 51. On August 26, 1921, Dr. Goodall was awarded the Distinguished Service Cross for " exceptionally meritorious and distinguished services in the performance of duties of great responsibility as Lieutenant Colonel, Medical Corps, U. S. A., in command of the gas hospital of the Justice Hospital Group in the American Expeditionary Forces during the World War."

Dr. Goodall collaborated with Dr. Otto Folin on " Saccharin and the Health of Man," with Dr. E. P. Joslin on " The Treatment of Diabetes Mellitus " and with Dr. Francis G. Bennett on " A Study of Prolonged Fasting " and " The War Diary of a Medical Officer," and by himself wrote authoritative works on thoracic stomach.

Dr. Goodall served on the staff of the Boston Dispensary, the New England Baptist Hospital, the New England Deaconess and the Palmer Memorial. He was a member of the Council of the Massachusetts Medical Society, a Fellow of the American College of Physicians (1931), a member of the American Medical Association, and belonged to the Masons, the Military Order of the World War, the Harvard Club of Boston, and the Square and Compass Club.

Dr. Goodall was married in 1925 to Emma Claflin Pierce of Boston who died in 1932. He leaves two brothers, George E. Goodall of Wells, Maine, and Frank R. Goodall of Exeter, New Hampshire.

WILLIAM B. BREED, M.D., F.A.C.P.,
Governor for Massachusetts

DR. FREDERICK EPPLEN

Dr. Frederick Epplen, Seattle, died suddenly in an attack of angina pectoris May 25, 1935, after an illness of over four years.

Dr. Epplen was born April 11, 1880, in Dennjacht, Germany. He began his medical education at the University of Nebraska and was graduated from Rush Medical College in 1906. After an internship in Cook County Hospital he practiced in Miles City, Montana, and in St Joe, Idaho. He then took postgraduate work in Vienna and located in Spokane for the practice of internal medicine. In 1927 he moved to Seattle and practiced there until disabled by illness in 1931.

During his years in Spokane and in Seattle he was an outstanding figure in the profession, of more than local prominence. He was always a deep student, and it was his constant effort to improve the plan of medical practice both in his own office and in the profession at large. He was always active in the various medical societies to which he belonged. The encouragement, advice, and friendly criticism which he was always ready to give will long be remembered by those who were fortunate enough to be associated with him.

He gave a great deal of time and work to the Pacific Northwest Medical Association, an organization for postgraduate instruction, and its success in the early years was due largely to his guidance. He was one of the organizers and the first president of the North Pacific Society of Internal Medicine, and lived to see it become active and vigorous, to his great happiness. He prized his membership in the Pacific Interurban Club, and made every effort to attend its meetings, even during his illness. The College has suffered a great loss in his death.

During the many years when he was Governor for Washington of the American College of Physicians, it seemed always foremost in his thoughts, and he worked constantly for the improvement of the College. He attended the Philadelphia Session in April of this year, knowing well before he went that his heart was in no condition for such a trip. His love for the associations and friendships of the College urged him on to attend this last meeting, even though it would be likely to hasten his death.

He is survived by his widow, Mrs. Ruth Merrill Epplen, a daughter, Miss Dorothy Epplen, of Claremont, Calif., and a brother, Carl Epplen in South Dakota.

CHARLES E. WATTS, M.D., F.A.C.P.,
Governor for Washington

DR. LOUIS F. JERMAIN

Dr. Louis F. Jermain, Dean Emeritus of the Marquette University School of Medicine, Milwaukee, Wisconsin, died on July 24, 1935, following a long illness.

Dr. Jermain was born in Manitowoc County, Wisconsin, in 1867. His preliminary education was obtained in local schools, following which he taught in a country school for seven years. At the age of twenty-four years he entered Northwestern University Medical School, from which he was graduated in 1894.

Upon his graduation Dr. Jermain came to Milwaukee where he joined the faculty of the old Wisconsin College of Physicians and Surgeons. He later became a member of the faculty of Marquette College and was largely responsible for the merging of that College with the Wisconsin College of Physicians and Surgeons in 1913, when he was appointed Dean of the Medical School, which office he held until the year 1926.

Dr. Jermain was assistant City Health Commissioner from 1908 to 1910. He became a member of The Medical Society of Milwaukee County on February 14, 1902, and in 1910 he was elected President. In 1916 he became President of the State Medical Society of Wisconsin. Upon the recommendation of Archbishop Sebastian G. Messmer, Dr. Jermain was made a Knight of the Order of St. Gregory the Great by Pope Pius XI in 1924.

Because of his contribution to medicine and long activity in the interests of the medical profession, Dr. Jermain was unanimously elected Honorary Member of The Medical Society of Milwaukee County on March 8, 1935. Dr. Jermain became a Fellow of the American College of Physicians during 1920.

ROCK SLEYSTER, M.D., F.A.C.P.,
Governor for Wisconsin

DR. FREDERICK RIGBY BARNES

Dr. Frederick Rigby Barnes (Fellow), born in Philadelphia, Pa., August 12, 1890, died July 18, 1935, in the Union Hospital, Fall River, Mass. He had been in poor health for two years, as a result of a staphylococcic infection of the blood stream following accidental puncture of a vein on the back of his hand with an infected hypodermic needle while treating a patient. During the last few months it appeared he would recover, and he had resumed practice.

Dr. Barnes attended Bucknell University and later obtained his medical degree at the University of Pennsylvania School of Medicine, graduating in 1913. He interned at the Chestnut Hill Hospital and then spent two years as resident physician and surgeon at the German (now the Lankenau) Hospital in Philadelphia.

In 1917 he went to Fall River, but early in the World War enlisted, attained the rank of captain, and served with the Pennsylvania (Philadelphia) Hospital unit at an English base in France. Dr. Barnes served as associate medical director for his district for eight years and in 1927 was appointed medical examiner by Governor Alvan T. Fuller. He was chief of the medical service at the Truesdale Hospital.

Dr. Barnes became a Fellow of the American College of Physicians during 1930, and promptly thereafter became a Life Member. He was the author of a number of published articles, and a man of wide reputation in his part of the country. He was a member of the Phi Gamma Delta and the Phi Alpha Sigma Fraternities, a past Secretary and past President of the Fall River Medical Society, a member and councillor of the Massachusetts Medical Society, a member of the Massachusetts Medico-Legal Society, and a Fellow of the American Medical Association.

DR. JOHN MASON MORRIS

Dr. John Mason Morris (Fellow), Louisville, Ky., was born April 25, 1861, at Sulphur, Ky., and died July 18, 1935, Louisville, Ky., at the age of seventy-four.

Dr. Morris was an outstanding example of a family physician and retained the fine traditions of the old time medical profession. He always had the interest of his patients at heart, regardless of their ability to remunerate him for his services. As a consequence, he has left behind a host of patients to mourn his death, as well as members of the medical profession of Louisville who respected him for his kindness of heart, his devotion to his profession and his loyalty to his friends.

He was a member of the American Medical Association, the Southern Medical Association, the Kentucky State Medical Association and its component societies, and he became a Fellow of the American College of Physicians in 1927.

C. W. Dowden, M.D., F.A.C.P.,
Governor for Kentucky

DR. THURSTON HOPKINS DEXTER

Dr. Thurston Hopkins Dexter (Fellow), Brooklyn, N. Y., died June 24, 1935, at the age of fifty-eight years. Dr. Dexter was born and educated in Brooklyn. He graduated from the Long Island College Hospital in 1901. His practice was devoted to pathology and bacteriology. He was pathologist and bacteriologist at the Methodist Episcopal Hospital, 1905–14; Williamsburg Hospital, 1907–10; Coney Island Hospital, 1908–11; Bushwick Hospital, 1909–15; Lutheran Hospital, 1909–17. At the time of his death he was chief pathologist at the Wyckoff Heights Hospital and the Swedish Hospital.

During the World War Dr. Dexter held the rank of Major and was in command of field hospitals of the 301st Sanitary Train, and later the 4th Corps Sanitary Train, serving in the Meuse-Argonne sector. After the war he was for seven years regimental surgeon of the 101st Cavalry, National Guard, and held the rank of lieutenant colonel in the Medical Reserve Corps.

He was the author of several published articles, a member of his county and state medical societies, a Fellow of the American Medical Association and ex-President of the Brooklyn Pathological Society, Brooklyn Hospital Club and Long Island College Alumni Association. He was also a member of the Associated Physicians of Long Island and the Association of Military Surgeons. He became a Fellow of the American College of Physicians during 1929. His burial took place at Arlington Cemetery, Washington.

DR. FRANKLIN WELKER

Dr. Franklin Welker (Fellow), New York, N. Y., died July 17, 1935, at his summer home in Highland, N. Y., of heart disease, at the age of sixty-eight years.

Dr. Welker was born at Attica, N. Y., July 20, 1867. He attended the University of Rochester, from which he received the degree of A.B., and then pursued his medical education at the University of Pennsylvania, graduating in 1894. He spent his internship at the Kings County Hospital, Brooklyn. For many years he was attending physician and medical director of the Lutheran Hospital of Manhattan, which appointment he held at the time of his death. He was President of the Medical Society of the County of New York, and a member of the New York Academy of Medicine, the Medical Association of Greater New York, the Harlem Medical Association, the Washington Heights Medical Society, the West Side Clinical Society, the National Tuberculosis Association and a Fellow of the American Medical Association. He became a Fellow of the American College of Physicians on December 1, 1923.

Dr. Welker was especially known as a physician who sought to uphold the position of the general practitioner in the medical profession. He was opposed to governmental encroachment in the field of medicine in competition with both private hospitals and individual physicians. He did not believe in compulsory health insurance plans, which would place the medical profession under the control of laymen and politicians. While he admitted the need for governmental hospitals, he felt they should not be permitted to submerge private institutions. At his induction as President of his county society, last January, he said in part, concerning compulsory insurance:

> Most, if not all, of the abuses connected with medical service in workmen's compensation have grown out of the suppression of the free choice of physicians, and investing the insurance carriers and employers with control over treatment. Business men chose the doctor, and their concern is cheap care, rather than good care. Under their egis commercial clinics have sprung up that harbor every evil that can come into healing—inefficiency, unnecessary prolongation of treatment, rebating, "lifting" of cases and padding of bills.

Dr. Welker was always a student. He was quiet and of even disposition, and was especially characterized by his thoughtfulness of others.

Surviving him are his wife, Mrs. Louise A. Welker and two daughters, Mrs. E. L. Rohdenburg and Miss Marian Welker.

DR. FRANCIS W. HEAGEY

Dr. Francis W. Heagey (Fellow), Omaha, Nebr., died August 23, 1935, of an embolism, one week after an appendectomy, aged fifty-one years.

Dr. Heagey was born at Bareville, Pa., attended Princeton University for his academic training, and graduated from Columbia University College of Physicians and Surgeons in 1912 with the degree of Doctor of Medicine. He practiced in New York City until 1916 when he went to Omaha to engage in practice and to become Instructor in Medicine at Creighton University School of Medicine. At the time of his death, he was Associate Professor of Medicine at Creighton University School of Medicine, Attending Physician to Creighton Memorial, St. Joseph's Hospital. He was a member of the Douglas County Medical Society, the Nebraska State Medical Association, a Fellow of the American Medical Association, and until recently president of the Nebraska State Tuberculosis Association.

Dr. Heagey was deeply interested in welfare work, a member of the State Emergency Relief Committee, and sometime president of the Omaha Child Welfare League and the Omaha Council of Social Agencies. He had contributed voluminously to medical literature, and was recognized as a man of distinctive worth to his community. He became a Fellow of the American College of Physicians in 1922.

DR. JESSIE WORTHY LEA

Dr. Jessie Worthy Lea (Fellow) of Jackson, Louisiana, died July 9, 1935, of coronary occlusion, aged 66.

Dr. Lea received his M.D. degree from Tulane University, Medical Department, in 1891. He was a member of the East and West Feliciana Parish Medical Society, Louisiana State Medical Society, the American Medical Association and in 1929 he was made a Fellow of the American College of Physicians.

He served as president of his local medical society, president and councilor of the Sixth District Medical Society. For eight years he served on the staff of the East Louisiana State Hospital, and also served as a member of the board of administrators of this institution.

Dr. Lea was a delightful personality who was loved and appreciated by his many friends. He is survived by his wife, Mrs. Grace M. Lea.

J. E. KNIGHTON, F.A.C.P.,
Governor for Louisiana